INDOLES USEFUL IN THE TREATMENT OF INFLAMMATION

Field of the Invention

This invention relates to novel pharmaceutically-useful compounds, which compounds are useful as inhibitors of microsomal prostaglandin E synthase-1 (mPGES-1). The compounds are of potential utility in the treatment of inflammatory diseases. The invention also relates to the use of such compounds as medicaments, to pharmaceutical compositions containing them, and to synthetic routes for their production.

Background of the Invention

There are many diseases/disorders that are inflammatory in their nature. One of the major problems associated with existing treatments of inflammatory conditions is a lack of efficacy and/or the prevalence of side effects (real or perceived).

Inflammatory diseases that affect the population include asthma, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, rhinitis, conjunctivitis and dermatitis.

Inflammation is also a common cause of pain. Inflammatory pain may arise for numerous reasons, such as infection, surgery or other trauma. Moreover, several malignancies are known to have inflammatory components adding to the symptomatology of the patients.

The cyclooxygenase (COX) enzyme exists in two forms, one that is constitutively expressed in many cells and tissues (COX-1), and one that is

induced by pro-inflammatory stimuli, such as cytokines during an inflammatory response (COX-2).

COXs metabolise arachidonic acid to the unstable intermediate prostaglandin H_2 (PGH_2). PGH_2 is further metabolized to other prostaglandins including PGE_2, $PGF_{2\alpha}$, PGD_2, prostacyclin and thromboxane A_2. These arachidonic acid metabolites are known to have pronounced physiological and pathophysiological activity including pro-inflammatory effects.

PGE_2 in particular is known to be a strong pro-inflammatory mediator, and is also known to induce fever and pain. Consequently, numerous drugs have been developed with a view to inhibiting the formation of PGE_2, including "NSAIDs" (non-steroidal antiinflammatory drugs) and "coxibs" (selective COX-2 inhibitors). These drugs act predominantly by inhibition of COX-1 and/or COX-2, thereby reducing the formation of PGE_2.

However, the inhibition of COXs has the disadvantage that it results in the reduction of the formation of all metabolites of arachidonic acid, some of which are known to have beneficial properties. In view of this, drugs which act by inhibition of COXs are therefore known/suspected to cause adverse biological effects. For example, the non-selective inhibition of COXs by NSAIDs may give rise to gastrointestinal side-effects and affect platelet and renal function. Even the selective inhibition of COX-2 by coxibs, whilst reducing such gastrointestinal side-effects, is believed to give rise to cardiovascular problems.

An alternative treatment of inflammatory diseases that does not give rise to the above-mentioned side effects would thus be of real benefit in the clinic.

In particular, a drug that inhibits (preferably selectively) the transformation of PGH_2 to the pro-inflammatory mediator PGE_2 might be expected to reduce the inflammatory response in the absence of a corresponding reduction of the formation of other, beneficial arachidonic acid metabolites. Such inhibition would accordingly be expected to alleviate the undesirable side-effects mentioned above.

PGH_2 may be transformed to PGE_2 by prostaglandin E synthases (PGES). Two microsomal prostaglandin E synthases (mPGES-1 and mPGES-2), and one cytosolic prostaglandin E synthase (cPGES) have been described.

mPGES-1 belongs to the membrane-associated proteins in the eicosanoid and glutathione metabolism (MAPEG) family. Other members of this family include the 5-lipoxygenase-activating protein (FLAP), leukotriene C_4 synthase and microsomal glutathione S-transferases (MGST1, MGST2 and MGST3).

Thus, agents that are capable of inhibiting the action of mPGESs and, in particular, mPGES-1, and thus reducing the formation of the specific arachidonic acid metabolite PGE_2, are likely to be of benefit in the treatment of inflammation.

Prior Art

Various indoles, and derivatives thereof, have been disclosed in international patent applications WO 01/30343, WO 96/03377 and WO 99/33800, US patents Nos. 5,189,054 and 6,525,083 and European patent application EP 483 881. However, none of these documents disclose or suggest the use of the compounds disclosed therein in the treatment of inflammation.

Structurally related indoles have been disclosed for potential use in the treatment of inflammation in international patent application WO 99/05104 and European patent application EP 985 666. However these documents do not disclose or suggest indoles that are substituted in the 1-position.

Other related indoles have been disclosed for potential use in the treatment of inflammation in international patent application WO 94/13662, US patent No. 5,081,145 and European patent application EP 535 924. However, none of these documents disclose or suggest indoles that are directly substituted at the benzenoid moiety of the indole ring with an aryl or heteroaryl group.

US patent No. 5,081,138 and European patent application EP 166 591 disclose indoles for potential use in the treatment of inflammation. However, neither of these documents disclose or suggest indoles that are directly substituted at the 2-position of the indole ring with a carboxylic acid group or a derivative thereof.

International patent applications WO 99/07351 and WO 99/07678 disclose indoles for potential use in the treatment of inflammation but do not disclose or suggest indoles that are substituted in the indolic 3-position by an aryl, a heteroaryl or an amide group.

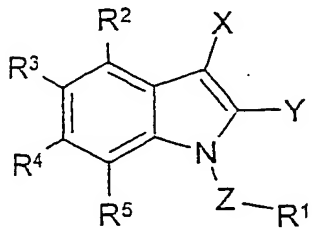
International patent applications WO 00/46198, WO 00/46197, WO 00/46195, WO 00/46199, WO 94/14434, WO 96/18393 and WO 02/30895 describe indole compounds for potential use in the treatment of inflammation. However, there is no specific disclosure in any of these documents of substitution at the benzenoid moiety of the indole ring with an aryl or heteroaryl group.

International patent applications WO 98/08818 and WO 99/43672 also disclose indoles for potential use in the treatment of inflammation. However, there is no specific disclosure in either of these documents of indoles substituted in the 3-position by an aryl or heteroaryl group, or a nitrogen derivative, such as an amine, amide or sulfonamide group attached to the indole ring through the nitrogen atom.

Finally, international patent applications WO 99/43654 and WO 99/43651 describe indole compounds for potential use in the treatment of inflammation. These documents do not specifically disclose indoles substituted in the 3-position by an aryl or heteroaryl group, or a nitrogen derivative, such as an amine, amide or sulfonamide group attached to the indole ring through the nitrogen atom, and which are further substituted at the benzenoid moiety of the indole ring with an aryl or heteroaryl group.

Disclosure of the Invention

According to the invention there is provided a compound of formula I,



I

wherein

X represents:

i) an aryl group or a heteroaryl group, both of which groups are optionally substituted by one or more substituents selected from A; or

ii) $-N(R^6)-E-R^7$;

E represents a single bond, $-C(O)-$ or $-S(O)_n-$;

Y represents $-CH_2OH$, $-C(O)N(H)R^8$, $-C(O)N(H)OR^8$ or $-C(O)OR^8$;

Z represents a C_{1-8} alkylene or a C_{2-8} heteroalkylene chain, both of which:

(i) optionally contain one or more unsaturations (for example double or triple bonds);

(ii) are optionally substituted by one or more substituents selected from halo, $-R^8$, $-N(R^8)(R^9)$, $-OR^8$ and =O; and/or

(iii) may form part of an additional 3- to 8-membered ring formed between any one or more (e.g. one or two) members of the C_{1-8} alkylene or C_{2-8} heteroalkylene chain, which ring optionally contains 1 to 3 heteroatoms and/or 1 to 3 unsaturations (for example double or triple bonds) and which ring is itself optionally substituted by one or more substituents selected from halo, $-R^8$, $-N(R^8)(R^9)$, $-OR^8$ and =O;

R^1 represents an aryl or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from A;

one of the groups R^2, R^3, R^4 and R^5 represents an aryl group or a heteroaryl group (both of which are optionally substituted by one or more substituents selected from A) and:

a) the other groups are independently selected from hydrogen, G^1, an aryl group, a heteroaryl group (which latter two groups are optionally substituted by one or more substituents selected from A), C_{1-6} alkyl, C_{3-10} (e.g. C_{3-8}) cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{3-8} heterocycloalkyl

(which latter five groups are optionally substituted by one or more substituents selected from G^1 and/or Q^1); and/or

b) any two other groups which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, a 5- to 6-membered ring, optionally containing 1 or more (e.g. 1 to 3) heteroatoms and/or 1 to 3 unsaturations (for example double or triple bonds), which ring is itself optionally substituted by one or more substituents selected from halo, $-R^8$, $-OR^8$ and =O;

A represents, on each occasion when mentioned above:

I) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from B;

II) a C_{1-6} alkyl, C_{3-10} (e.g. C_{3-8}) cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{3-8} heterocycloalkyl group, all of which are optionally substituted by one or more substituents selected from G^1 and/or Q^1; or

III) a G^1 group; or

IV) two adjacent A substituents may be linked together to form, along with the essential atoms of the aryl or heteroaryl group to which the two A substituents are attached, a further 5- to 6-membered ring, optionally containing 1 or more (e.g. 1 to 3) heteroatoms and/or 1 to 3 unsaturations (for example double or triple bonds), which ring is itself optionally substituted by one or more substituents selected from halo, $-R^8$, $-OR^8$ and =O;

G^1 represents, on each occasion when mentioned above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^1-R^{10}$;

wherein A^1 represents a single bond or a spacer group selected from $-C(Q^2)A^2-$, $-S(O)_nA^3-$, $-N(R^{11})A^4-$, $-OA^5-$ and $-S-$, in which:

A^2 represents A^6 or $-S-$;

A^3 represents A^6;

A^4 represents A^7, $-C(Q^2)N(R^{11})C(Q^2)N(R^{11})-$, $-C(Q^2)N(R^{11})C(Q^2)O-$, $-C(Q^2)N(R^{11})S(O)_nN(R^{11})-$, $-C(Q^2)S-$, $-S(O)_nN(R^{11})C(Q^2)N(R^{11})-$, $-S(O)_nN(R^{11})C(Q^2)O-$, $-S(O)_nN(R^{11})S(O)_nN(R^{11})-$ or $-S(O)_nO-$;

A^5 represents A^7 or $-S(O)_nO-$;

A^6 represents a single bond, $-N(R^{11})-$ or $-O-$;

A^7 represents a single bond, $-C(Q^2)-$, $-C(Q^2)N(R^{11})-$, $-C(Q^2)O-$, $-S(O)_n-$ or $-S(O)_nN(R^{11})$;

Q^1 and Q^2 independently represent, on each occasion when mentioned above, $=O$, $=S$, $=NR^{10}$, $=NN(R^{10})(R^{11})$, $=NOR^{10}$, $=NS(O)_2N(R^{10})(R^{11})$, $=NCN$, $=C(H)NO_2$ or $=C(R^{10})(R^{11})$;

R^6 and R^7 independently represent, on each occasion when mentioned above:

I) hydrogen;

II) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from B; or

III) a C_{1-6} alkyl, C_{3-10} (e.g. C_{3-8}) cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{3-8} heterocycloalkyl group, all of which groups are optionally substituted by one or more substituents selected from G^2 and/or Q^3; or

R^6 and R^7 may be linked together to form along with the N atom and –E- group to which R^6 and R^7 are respectively attached, a 5- to 8-membered ring, optionally containing 1 to 3 heteroatoms and/or 1 to 3 unsaturations (for example double or triple bonds), which ring is optionally substituted by one or more substituents selected from G^2 and/or Q^3;

B represents, on each occasion when mentioned above:

I) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from G^2 and/or wherein any two adjacent atoms of the aryl or heteroaryl group may be linked together to

form a further 5- to 6-membered ring, optionally containing 1 or more (e.g. 1 to 3) heteroatoms and/or 1 to 3 unsaturations (for example double or triple bonds), which ring is itself optionally substituted by one or more substituents selected from halo, $-R^8$, $-OR^8$ and =O;

II) a C_{1-6} alkyl, C_{3-10} (e.g. C_{3-8}) cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{3-8} heterocycloalkyl group, all of which are optionally substituted by one or more substituents selected from G^2 and/or Q^3; or

III) a G^2 group; or

IV) two adjacent B substituents may be linked together to form, along with the essential atoms of the aryl or heteroaryl group to which the two B substituents are attached, a further 5- to 6-membered ring, optionally containing 1 or more (e.g. 1 to 3) heteroatoms and/or 1 to 3 unsaturations (e.g. double or triple bonds), which ring is itself optionally substituted by one or more substituents selected from halo, $-R^8$, $-OR^8$ and =O;

G^2 represents, on each occasion when mentioned above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^8-R^{12}$;

wherein A^8 represents a single bond or a spacer group selected from $-C(Q^4)A^9-$, $-S(O)_nA^{10}-$, $-N(R^{13})A^{11}-$, $-OA^{12}-$ and $-S-$, in which:

A^9 represents A^{13} or $-S-$;

A^{10} represents A^{13};

A^{11} represents A^{14}, $-C(Q^4)N(R^{13})C(Q^4)N(R^{13})-$, $-C(Q^4)N(R^{13})C(Q^4)O-$, $-C(Q^4)N(R^{13})S(O)_nN(R^{13})-$, $-C(Q^4)S-$, $-S(O)_nN(R^{13})C(Q^4)N(R^{13})-$, $-S(O)_nN(R^{13})C(Q^4)O-$, $-S(O)_nN(R^{13})S(O)_nN(R^{13})-$ or $-S(O)_nO-$;

A^{12} represents A^{14} or $-S(O)_nO-$;

A^{13} represents a single bond, $-N(R^{13})-$ or $-O-$;

A^{14} represents a single bond, $-C(Q^4)-$, $-C(Q^4)N(R^{13})-$, $-C(Q^4)O-$, $-S(O)_n-$ or $-S(O)_nN(R^{13})$;

Q^3 and Q^4 independently represent, on each occasion when mentioned above, =O, =S, $=NR^{12}$, $=NN(R^{12})(R^{13})$, $=NOR^{12}$, $=NS(O)_2N(R^{12})(R^{13})$, =NCN, $=C(H)NO_2$ or $=C(R^{12})(R^{13})$;

R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are independently selected from:

i) hydrogen;

ii) an aryl or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from G^3 and/or wherein any two adjacent atoms of the aryl or heteroaryl group may be linked together to form a further 5- to 6-membered ring, optionally containing 1 or more (e.g. 1 to 3) heteroatoms, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^{14}$, $-OR^{14}$ and =O; or

iii) a C_{1-6} alkyl, C_{3-10} (e.g. C_{3-8}) cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{3-8} heterocycloalkyl group, all of which are optionally substituted by one or more substituents selected from G^3 and/or W^1; or

any pair of R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} may, for example when present on the same or on adjacent atoms, be linked together to form with those, or other relevant, atoms, a further 5- to 8-membered ring, optionally containing 1 to 3 heteroatoms and/or 1 to 3 unsaturations (for example double or triple bonds), which ring is itself optionally substituted by one or more substituents selected from G^3 and/or W^1;

G^3 represents, on each occasion when mentioned above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^{15}-R^{15}$;

wherein A^{15} represents a single bond or a spacer group selected from $-C(W^2)A^{16}-$, $-S(O)_nA^{17}-$, $-N(R^{16})A^{18}-$, $-OA^{19}-$ and $-S-$, in which:

A^{16} represents A^{20} or $-S-$;

A^{17} represents A^{20};

A^{18} represents A^{21}, $-C(W^2)N(R^{16})C(W^2)N(R^{16})-$, $-C(W^2)N(R^{16})C(W^2)O-$, $-C(W^2)N(R^{16})S(O)_nN(R^{16})-$, $-C(W^2)S-$, $-S(O)_nN(R^{16})C(W^2)N(R^{16})-$, $-S(O)_nN(R^{16})C(W^2)O-$, $-S(O)_nN(R^{16})S(O)_nN(R^{16})-$ or $-S(O)_nO-$;

A^{19} represents A^{21} or $-S(O)_nO-$;

A^{20} represents a single bond, $-N(R^{16})-$ or $-O-$;

A^{21} represents a single bond, $-C(W^2)-$, $-C(W^2)N(R^{16})-$, $-C(W^2)O-$, $-S(O)_n-$ or $-S(O)_nN(R^{16})$;

W^1 and W^2 independently represent, on each occasion when mentioned above, =O, =S, $=NR^{15}$, $=NN(R^{15})(R^{16})$, $=NOR^{15}$, $=NS(O)_2N(R^{15})(R^{16})$, =NCN, $=C(H)NO_2$ or $=C(R^{15})(R^{16})$;

R^{14}, R^{15} and R^{16} are independently selected from:

i) hydrogen;

ii) an aryl or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from G^4, methylenedioxy, difluoromethylenedioxy and/or dimethylmethylenedioxy; or

iii) a C_{1-6} alkyl, C_{3-10} (e.g. C_{3-8}) cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{3-8} heterocycloalkyl group, all of which are optionally substituted by one or more substituents selected from G^4 and/or J; or

any pair of R^{14}, R^{15} and R^{16} may, for example when present on the same or on adjacent atoms, be linked together to form with those, or other relevant, atoms, a further 5- to 7-membered ring, optionally containing 1 to 3 heteroatoms and/or 1 to 3 unsaturations (for example double or triple bonds), which ring is itself optionally substituted by one or more substituents selected from G^4 and J;

G^4 represents, on each occasion when mentioned above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^{22}-R^{17}$;

wherein A^{22} represents a single bond or a spacer group selected from $-C(O)A^{23}-$, $-S(O)_nA^{24}-$, $-N(R^{18})A^{25}-$, $-OA^{26}-$ and –S-, in which:

A^{23} represents A^{27} or –S-;

A^{24} represents A^{27};

A^{25} represents A^{28}, $-C(O)N(R^{18})C(O)N(R^{18})-$, $-C(O)N(R^{18})C(O)O-$, $-C(O)N(R^{18})S(O)_nN(R^{18})-$, $-C(O)S-$, $-S(O)_nN(R^{18})C(O)N(R^{18})-$, $-S(O)_nN(R^{18})C(O)O-$, $-S(O)_nN(R^{18})S(O)_nN(R^{18})-$ or $-S(O)_nO-$;

A^{26} represents A^{28} or $-S(O)_nO-$;

A^{27} represents a single bond, $-N(R^{18})-$ or –O-;

A^{28} represents a single bond, -C(O)-, $-C(O)N(R^{18})-$, -C(O)O-, $-S(O)_n-$ or $-S(O)_nN(R^{18})$;

J represents, on each occasion when mentioned above, =O, =S, $=NR^{17}$, $=NN(R^{17})(R^{18})$, $=NOR^{17}$, $=NS(O)_2N(R^{17})(R^{18})$, =NCN, $=C(H)NO_2$ or $=C(R^{17})(R^{18})$;

R^{17} and R^{18} are independently selected from hydrogen and C_{1-6} alkyl, which latter group is optionally substituted by one or more substituents selected from halo, $-NH_2$, -N(H)Me, -N(H)Et, -N(H)*i*-Pr, $-NMe_2$, -N(Me)Et, -N(Me)*i*-Pr, $-NEt_2$, -OH, -OMe, -OEt, -O*i*-Pr and =O; and

n represents, on each occasion when mentioned above, 1 or 2,

or a pharmaceutically-acceptable salt thereof,

which compounds and salts are referred to hereinafter as "the compounds of the invention".

Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for

example by reaction of a free acid or a free base form of a compound of the invention with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

Compounds of the invention may contain double bonds and may thus exist as *E* (*entgegen*) and *Z* (*zusammen*) geometric isomers about each individual double bond. All such isomers and mixtures thereof are included within the scope of the invention.

Compounds of the invention may also exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation (i.e. a 'chiral pool' method), by reaction of the appropriate starting material with a 'chiral auxiliary' which can subsequently be removed at a suitable stage, by derivatisation (i.e. a resolution, including a dynamic resolution), for example with a homochiral acid followed by separation of the

diastereomeric derivatives by conventional means such as HPLC or chromatography over silica, or by reaction with an appropriate chiral reagent or chiral catalyst all under conditions known to the skilled person. All stereoisomers and mixtures thereof are included within the scope of the invention.

Unless otherwise specified, C_{1-q} alkyl groups (where q is the upper limit of the range) defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of three) of carbon atoms, be branched-chain. C_{1-6} alkyl groups that may be mentioned include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, isopentyl, *n*-hexyl, and isohexyl.

C_{1-q} alkylene chains (where q is the upper limit of the range) defined herein are straight-chain alkyl groups, which groups are attached at each terminal end.

C_{v-q} heteroalkylene chains (where v is the lower limit and q is the upper limit of the range) defined herein are C_{v-q} alkylene chains, wherein one or more (e.g. 1 to q-1) carbon atoms have been replaced with a heteroatom.

C_{2-q} alkenyl groups (where q is the upper limit of the range) defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of three) of carbon atoms, be branched-chain. Such alkenyl groups may contain one or more double bonds. C_{2-6} alkenyl groups that may be mentioned include ethenyl (i.e. vinyl), 1-propenyl, 2-propenyl (i.e. allyl), propadienyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,3-butadienyl, 1-pentenyl, 2-pentenyl, 4-pentenyl, and 5-hexenyl.

C_{2-q} alkynyl groups (where q is the upper limit of the range) defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of four) of carbon atoms, be branched-chain. Such alkynyl groups may contain one or more triple bonds. C_{2-6} alkynyl groups that may be mentioned include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, and 5-hexynyl.

C_{3-q} cycloalkyl groups (where q is the upper limit of the range) that may be mentioned include monocyclic or bicyclic alkyl groups, or fused ring systems such as three fused cycloalkyl groups. Such cycloalkyl groups may be saturated or unsaturated containing one or more double or triple bond (forming for example a C_{3-q} cycloalkenyl or a C_{3-q} cycloalkynyl group). C_{3-q} (e.g. C_{3-10}) cycloalkyl groups that may be mentioned include adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclooctynyl, bicycloheptyl, bicyclooctyl, and bicyclooctenyl. Substituents may be attached at any point on the cycloalkyl group. Further in the case where the substituent is another cyclic compound, then the cyclic substituent may be attached through a single atom on the cycloalkyl group, forming a so-called "spiro"-compound.

C_{3-q} heterocycloalkyl groups (where q is the upper limit of the range) that may be mentioned include monocyclic or bicyclic alkyl groups in which at least one (e.g. one to four) of the atoms in the ring system is other than carbon (i.e. a hetereoatom). Further, such heterocycloalkyl groups may be saturated or unsaturated containing one or more double and/or triple bonds, forming for example a C_{3-q} heterocycloalkenyl or a C_{3-q} heterocycloalkynyl group. C_{3-q} heterocycloalkyl groups that may be mentioned include aziridinyl, azetidinyl, dihydropyranyl, dihydropyridyl, dihydropyrrolyl

(including 2,5-dihydropyrrolyl), dioxolanyl (including 1,3-dioxolanyl), dioxanyl (including 1,3-dioxanyl and 1,4-dioxanyl), dithianyl (including 1,4-dithianyl), dithiolanyl (including 1,3-dithiolanyl), imidazolidinyl, imidazolinyl, morpholinyl, oxetanyl, oxiranyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, sulfolanyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydropyridyl, thietanyl, thiiranyl, thiolanyl, thiomorpholinyl, trithianyl (including 1,3,5-trithianyl), tropanyl and the like. Substituents on the heterocycloalkyl groups may, where appropriate, be located on any atom in the ring system including a heteroatom. Further in the case where the substituent is another cyclic compound, then the cyclic substituent may be attached through a single atom on the heterocycloalkyl group, forming a so-called "spiro"-compound. The point of attachment of a heterocycloalkyl group may be *via* any atom in the ring system including (where appropriate) a heteroatom, or an atom on any fused carbocyclic ring that may be present as part of the ring system. Heterocycloalkyl groups may also be in the *N*- or *S*- oxidised form.

The term "halo", when used herein, includes fluoro, chloro, bromo and iodo.

Aryl groups that may be mentioned include C_{6-13} aryl (e.g. C_{6-10}) groups. Such groups may be monocyclic, bicyclic or tricylic and have between 6 and 13 ring carbon atoms, in which at least one ring is aromatic. C_{6-13} aryl groups include phenyl, naphthyl and the like, such as 1,2,3,4-tetrahydro-naphthyl, indanyl, indenyl and fluorenyl. The point of attachment of aryl groups may be *via* any atom of the ring system.

Heteroaryl groups that may be mentioned include those which have between 5 and 10 members. Such groups may be monocyclic, bicyclic or tricyclic, in which at least one of the rings is aromatic and wherein at least one (e.g.

one to four) of the atoms in the ring system is other than carbon (i.e. a heteroatom). Heteroaryl groups that may be mentioned include acridinyl, benzimidazolyl, benzodioxanyl, benzodioxepinyl, benzodioxolyl (including 1,3-benzodioxolyl), benzofuranyl, benzofurazanyl, benzothiazolyl (including 2,1,3-benzothiazolyl), benzoxadiazolyl (including 2,1,3-benzoxadiazolyl), benzoxazinyl (including 3,4-dihydro-2*H*-1,4-benzoxazinyl), benzoxazolyl, benzimidazolyl, benzomorpholinyl, benzoselenadiazolyl (including 2,1,3-benzoselenadiazolyl), benzothienyl, carbazolyl, chromanyl, cinnolinyl, furanyl, imidazolyl, imidazo[1,2-*a*]pyridyl, indazolyl, indolinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl (including 1,5-naphthyridinyl and 1,8-naphthyridinyl), oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl and 1,3,4-oxadiazolyl), oxazolyl, phenazinyl, phenothiazinyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrahydroisoquinolinyl (including 1,2,3,4-tetrahydroisoquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl), tetrahydroquinolinyl (including 1,2,3,4-tetrahydroquinolinyl and 5,6,7,8-tetrahydroquinolinyl), tetrazolyl, thiadiazolyl (including 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl and 1,3,4-thiadiazolyl), thiazolyl, thiochromanyl, thienyl, triazolyl (including 1,2,3-triazolyl, 1,2,4-triazolyl and 1,3,4-triazolyl) and the like. The point of attachment of heteroaryl groups may be *via* any atom in the ring system including (where appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring system. Heteroaryl groups may also be in the *N*- or *S*- oxidised form.

Heteroatoms that may be mentioned include oxygen, nitrogen, sulphur and selenium.

For the avoidance of doubt, optionally substituted methylenedioxy groups, when attached to a ring system, are formed between any two adjacent atoms of the ring system.

For the avoidance of doubt, in cases in which the identity of two or more substituents in a compound of the invention may be the same, the actual identities of the respective substituents are not in any way interdependent. For example, in the situation in which R^1 and R^3 are both aryl groups substituted by one or more C_{1-6} alkyl groups, the alkyl groups in question may be the same or different. Similarly, when groups are substituted by more than one substituent as defined herein, the identities of those individual substituents are not to be regarded as being interdependent. For example, when X and/or R^1 represents e.g. an aryl group substituted by G^1 in addition to, for example, C_{1-6} alkyl, which latter group is substituted by G^1, the identities of the two G^1 groups are not to be regarded as being interdependent.

Compounds that may be mentioned include those in which:

E represents –C(O)-;

when any two adjacent R^2, R^3, R^4 or R^5 groups, adjacent A substituents, adjacent B substituents, and/or, when B represents aryl or heteroaryl, adjacent atoms of those aryl or heteroaryl groups are linked to form a 5- to 6-membered ring, then that ring is fully saturated.

Preferred compounds of the invention include those in which:

Y represents $-CH_2OH$ or, more preferably, $-C(O)N(H)R^8$, $-C(O)N(H)OR^8$ or $-C(O)OR^8$;

A^8 represents a single bond, $-C(Q^4)A^9-$, $-S(O)_nA^{10}-$, $-N(R^{13})A^{11}-$ or $-OA^{12}-$;

A^9 represents A^{13};

A^{11} represents A^{14};

Q^3 represents =O, $=NN(R^{12})(R^{13})$, $=NOR^{12}$, $=NS(O)_2N(R^{12})(R^{13})$, =NCN or $=C(H)NO_2$;

Q^4 represents =O;

A^{15} represents a single bond, $-C(W^2)A^{16}$-, $-S(O)_nA^{17}$-, $-N(R^{16})A^{18}$- or $-OA^{19}$-:

A^{16} represents A^{20};

A^{18} represents A^{21};

W^1 represents =O, $=NN(R^{15})(R^{16})$, $=NOR^{15}$, $=NS(O)_2N(R^{15})(R^{16})$, =NCN or $=C(H)NO_2$;

W^2 represents =O;

when any pair of R^{14}, R^{15} and R^{16} is linked together to form a further optionally substituted 5- to 7-membered ring, then that ring optionally contains only 1 unsaturation;

A^{22} represents a single bond, $-C(O)A^{23}$-, $-S(O)_nA^{24}$-, $-N(R^{18})A^{25}$- or $-OA^{26}$-;

A^{23} represents A^{27};

A^{25} represents A^{28}; and/or

J represents =O, $=NN(R^{17})(R^{18})$, $=NOR^{17}$, $=NS(O)_2N(R^{17})(R^{18})$, =NCN, or $=C(H)NO_2$;

More preferred compounds of the invention include those in which:

Y represents $-CH_2OH$ or, more preferably, $-C(O)N(H)R^8$ or $-C(O)OR^8$;

when any two members of the C_{1-8} alkylene or C_{2-8} heteroalkylene chain that Z may represent form part of an additional optionally substituted 3- to 8-membered ring, then that ring optionally contains 1 to 2 heteroatoms and/or 1 unsaturation;

A^1 represents –S- or, more preferably, a single bond, $-C(Q^2)A^2$-, $-S(O)_nA^3$-, $-N(R^{11})A^4$- or $-OA^5$-:

A^2 represents A^6;

A^4 represents A^7;

Q^1 represents =O, $=NOR^{10}$, $=NS(O)_2N(R^{10})(R^{11})$, =NCN or $=C(H)NO_2$;

Q^2 represents =O;

when two adjacent atoms of the optionally substituted aryl or heteroaryl group that B may represent are linked together to form a further optionally substituted ring, then the linking divalent substituent that forms part of that ring is selected from methylenedioxy, difluoromethylenedioxy and dimethylmethylenedioxy;

Q^3 represents =O, $=NOR^{12}$, $=NS(O)_2N(R^{12})(R^{13})$, =NCN or $=C(H)NO_2$;

when R^6 and R^7 are linked to form an optionally substituted 5- to 8-membered ring, then that ring optionally contains only 1 unsaturation;

when two adjacent atoms of the optionally substituted aryl or heteroaryl group that R^8, R^9, R^{10}, R^{11}, R^{12} and/or R^{13} may represent are linked together to form a further optionally substituted ring, then the linking divalent substituent that forms part of that ring is selected from methylenedioxy, difluoromethylenedioxy and dimethylmethylenedioxy;

W^1 represents =O, $=NOR^{15}$, $=NS(O)_2N(R^{15})(R^{16})$, =NCN or $=C(H)NO_2$; and/or

R^{14}, R^{15} and R^{16} independently represent an aryl or heteroaryl group, both of which groups are optionally substituted by one or more substituents selected from halo, $-NH_2$, -N(H)Me, -N(H)Et, -N(H)*i*-Pr, $-NMe_2$, -N(Me)Et, -N(Me)*i*-Pr, $-NEt_2$, -OH, -OMe, -OEt, -O*i*-Pr and =O or, R^{14}, R^{15} and R^{16} are, more preferably, hydrogen or C_{1-6} alkyl, which latter group is optionally substituted by one or more substituents selected from halo, $-NH_2$, -N(H)Me, -N(H)Et, -N(H)*i*-Pr, $-NMe_2$, -N(Me)Et, -N(Me)*i*-Pr, $-NEt_2$, -OH, -OMe, -OEt, -O*i*-Pr and =O;

More preferred compounds include those in which:

Y represents $-CH_2OH$, $-C(O)NHR^8$ or, more preferably, $-C(O)OR^8$;

when any one or more members of the C_{1-8} alkylene or C_{2-8} heteroalkylene chain that Z may represent form part of an additional ring, then that ring is a

cyclopropyl group formed together with the same or adjacent carbon atoms of that C_{1-8} alkylene or C_{2-8} heteroalkylene chain;

when any adjacent pair of R^2, R^3, R^4 or R^5 is linked, to form an optionally substituted ring, then the linking divalent substituent that forms part of that ring is a methylenedioxy, difluoromethylenedioxy or dimethylmethylenedioxy group;

when any two adjacent A substituents are linked to form an optionally substituted ring, then the linking divalent substituent that forms part of that ring is selected from methylenedioxy, difluoromethylenedioxy and dimethylmethylenedioxy;

when any two adjacent B substituents are linked to form an optionally substituted ring, then the linking divalent substituent that forms part of that ring is selected from methylenedioxy, difluoromethylenedioxy and dimethylmethylenedioxy;

when R^6 and R^7 are linked to form an optionally substituted ring, then that ring is a 5- to 6-membered ring;

when any pair of R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} is linked to form a further optionally substituted ring, then that ring optionally contains only 1 unsaturation; and/or

n represents 2;

Preferred compounds of the invention include those in which R^1, and (when they represent an aryl or a heteroaryl group) X, R^2, R^3, R^4 and/or R^5 represent an optionally substituted fluorenyl, phenyl, naphthyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl (e.g. 2-pyridyl, 3-pyridyl or 4-pyridyl), indazolyl, indolyl, indolinyl, isoindolinyl, quinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinolizinyl, benzofuranyl, isobenzofuranyl, chromanyl, benzothienyl, pyridazinyl, pyrimidinyl, pyrazinyl, indazolyl,

benzimidazolyl, quinazolinyl, quinoxalinyl, 1,3-benzodioxolyl, benzothiazolyl, and/or benzodioxanyl, group

Preferred values of R^1 include optionally substituted fluorenyl (e.g. 2-fluorenyl) or pyridyl and, especially, optionally substituted phenyl.

Preferred values of X, when X represents an optionally substituted aryl or heteroaryl group include optionally substituted phenyl, thienyl (e.g. 2-thienyl), pyridyl (e.g. 3-pyridyl and 4-pyridyl), pyrazolyl, pyrazinyl or quinolinyl.

Preferred values of R^2, R^3, R^4 and R^5, when they represent an optionally substituted aryl or heteroaryl group, include optionally substituted phenyl, pyridyl (e.g. 3-pyridyl) or naphthyl (e.g. 1-naphthyl).

Further preferred compound of the invention include those in which:

Z represents C_{1-6} alkylene, such as methylene, propylene or hexylene, in which one of the carbon atoms in the chain may be replaced with a heteroatom (e.g. oxygen) so forming, for example, an oxypentylene group;

R^2 represents hydrogen or G^1;

R^3 represents hydrogen, phenyl or pyridyl (e.g. 3-pyridyl), which latter two groups are optionally substituted by one or more substituents selected from A;

R^4 represents hydrogen, phenyl or naphthyl, which latter two groups are optionally substituted by one or more substituents selected from A;

R^5 represents hydrogen or phenyl, which latter group is optionally substituted by one or more substituents selected from A or is preferably unsubstituted;

when R^2, R^3, R^4 or R^5 represents an optionally substituted phenyl, pyridyl or naphthyl group, then the other substituents on the essential benzene ring of

the indole of formula I, (i.e. R^2, R^3, R^4 or R^4 (as appropriate)) represent hydrogen or G^1;

A represents G^1 or any two adjacent A substituents may be linked to form a further ring, wherein the linking divalent substituent that forms part of that ring is preferably methylenedioxy, which group is preferably unsubstituted;

G^1 represents halo (such as chloro or fluoro), cyano, $-NO_2$ or $-A^1-R^{10}$;

A^2 represents A^6;

A^3 represents a single bond;

A^4 represents A^7;

A^5 represents A^7 and, preferably, a single bond;

A^7 represents a single bond, $-C(Q^2)-$ or $-S(O)_2-$;

Q^2 represents =O;

R^6 represents hydrogen or C_{1-3} alkyl group (such as methyl or ethyl), which latter group is optionally substituted by G^2;

R^7 represents an aryl group (such as phenyl) or a heteroaryl group (such as pyridyl), which latter two groups are optionally substituted by one or more substituents selected from B, or R^7 represents C_{1-4} alkyl (such as methyl, ethyl, propyl, butyl (e.g. *n*-butyl or *t*-butyl)), C_{2-4} alkenyl (such as ethenyl) or C_{5-10} cycloalkyl (such as cyclohexyl or adamantyl), which latter three groups are optionally substituted by one or more substituents selected from G^2; or

R^6 and R^7 are optionally linked to form a 5- to 6-membered ring optionally substituted by =O;

B represents G^2;

G^2 represents halo (such as chloro or fluoro), cyano, $-NO_2$ or $-A^8-R^{12}$;

A^8 represents a single bond, $-N(R^{13})A^{11}-$ or $-OA^{12}-$;

A^{11} and A^{12} independently represent A^{14};

A^{14} represents a single bond;

R^8 represents C_{1-3} alkyl (such as ethyl) or, preferably, hydrogen;

R^{10} represents hydrogen, aryl (such as phenyl), heteroaryl (such as tetrazolyl), C_{1-4} alkyl (such as methyl, ethyl, isopropyl or butyl (e.g. *n*-butyl or *t*-butyl)), C_{2-4} alkenyl (such as ethenyl or butenyl (e.g. but-3-enyl)) or C_{5-6} cycloalkyl (such as cyclohexyl), which latter five groups are optionally substituted by one or more substituents selected from G^3;

R^{11} represents hydrogen or C_{2-4} alkenyl (such as propenyl (e.g. propen-2-yl, i.e. allyl));

R^{12} represents hydrogen, an aryl group (such as a phenyl group), a heteroaryl group (such as a pyrrolyl group), C_{1-4} alkyl (such as methyl, isopropyl or butyl (e.g. *n*-butyl or *t*-butyl)) or C_{5-10} cycloalkyl (such as cyclohexyl or adamantyl) which latter four groups are optionally substituted by one or more substituents selected from G^3;

R^{13} represents hydrogen or C_{1-3} alkyl (such as methyl);

G^3 represents halo (such as fluoro) or $-A^{15}-R^{15}$;

A^{15} represents a single bond or $-OA^{19}-$;

A^{19} represents a single bond;

R^{15} represents hydrogen, C_{1-3} alkyl (such as C_{1-2} alkyl (e.g. methyl)) or aryl (such as phenyl).

Preferred optional substituents on R^1, R^6, R^7 and (when they represent an aryl or heteroaryl group) X, R^2, R^3, R^4 and R^5 groups are selected from:

halo (e.g. chloro, fluoro or bromo);

$-NO_2$;

cyano;

methylenedioxy;

C_{1-6} alkyl, which alkyl group may be linear or branched (e.g. C_{1-4} alkyl (including methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, isobutyl or *t*-butyl), *n*-pentyl, isopentyl, *n*-hexyl or isohexyl), and which alkyl groups are optionally substituted by one or more substituents selected from a halo (e.g.

fluoro) group (so forming, for example, $-CH_2F$, $-CHF_2$ or $-CF_3$), an aryl group (such as phenyl) and OR^{19};

C_{2-6} alkenyl (e.g. ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 4-pentenyl or 5-hexenyl);

C_{3-10} (e.g. C_{3-8}) cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cyclooctyl), optionally substituted with C_{1-6} alkyl (such as methyl);

phenyl, optionally substituted with one or more substituents selected from halo (e.g. fluoro or, especially, chloro) and OR^{19};

a heteroaryl group selected from tetrazolyl and pyrrolyl, optionally substituted by one or more C_{1-6} alkyl group (such as methyl);

methylthio, methylsulfinyl, methylsulfonyl;

=O;

$-OR^{19}$;

$-N(R^{19})R^{20}$;

$-C(O)OR^{19}$;

$-C(O)R^{19}$;

$-C(O)N(R^{19})R^{20}$;

$-S(O)_2N(R^{19})R^{20}$; and/or

$-N(R^{19})S(O)_2R^{21}$;

wherein R^{19} and R^{20} independently represent, on each occasion when used above, hydrogen, phenyl, C_{1-4} alkenyl (such as propenyl (e.g. propen-2-yl, i.e. allyl) or butenyl (e.g. but-3-enyl)), C_{1-6} alkyl (such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl or *t*-butyl) which alkyl group is optionally substituted by one or more fluoro atoms or a phenyl group;

R^{21} represents phenyl or C_{1-6} alkyl (such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl or *t*-butyl), which alkyl group is optionally substituted by one or more fluoro atoms.

When X represents an aryl or a heteroaryl group, then the substituents on such groups are preferably selected from carboxy, acetyl, methoxy, $-NO_2$, fluoro, methyl, chloro, hydroxymethyl, ethyl, isopropoxy, trifluoromethoxy and methylthio.

Preferred optional substituents on R^1 groups include phenoxy, trifluoromethyl, nitro, fluoro, chloro, cyano, carbamoyl, trifluoromethoxy, tetrazolyl (e.g. 2*H*-tetrazol-5-yl) and methyl.

When they represent an aryl or heteroaryl group, preferred optional substituents on R^2, R^3, R^4 or R^5 groups include *t*-butyl, methylenedioxy, benzyloxy, nitro, methoxy, acetyl, chloro, fluoro, *N*-allyl-*N*-methanesulfonyl, cyano, trifluoromethyl, 2,2-dimethylpropionylamino, methanesulfonylamino, amino, but-3-enylamino, isopropoxy, methylthio, methylsulfonyl, ethenyl (i.e. vinyl), trifluoromethoxy, cyclohexyl, *n*-butyl, carboxy and hydroxymethyl.

Preferred optional substituents on R^6 (when R^6 does not represent hydrogen and is not linked to form a ring with R^7) include an optionally substituted phenyl group. Optional substituents on such phenyl groups include halo (especially fluoro) and C_{1-3} alkoxy (such as methoxy), which substituents are preferably in the 4-position of the phenyl ring.

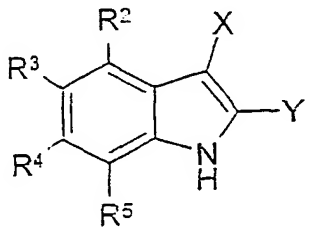
Preferred optionally substituents on R^7 (when R^7 is not linked to form a ring with R^6) include chloro, methoxy, amino, methyl, dimethylamino, phenyl, 4-methoxyphenyl, adamantyl, cyclohexyl, 3,3,5,5-tetramethylcyclohexyl, isopropoxy, trifluoromethyl, *t*-butyl, *n*-butyl, isopropyl, trifluoromethoxy, cyano, pyrrole (e.g. 2,5-dimethylpyrrole) and nitro.

Particularly preferred compounds of the invention include those of the examples described hereinafter.

Compounds of the invention may be made in accordance with techniques that are well known to those skilled in the art, for example as described hereinafter.

According to a further aspect of the invention there is provided a process for the preparation of a compound of formula I, which process comprises:

(i) reaction of a compound of formula II,



II

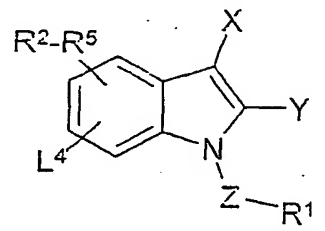
wherein X, Y, R^2, R^3, R^4 and R^5 are as hereinbefore defined, with a compound of formula III,

$$R^1ZL^1 \qquad \text{III}$$

wherein L^1 represents a suitable leaving group, such as halo (e.g. chloro, bromo or iodo), a carboxylate group, a sulfonylate group (e.g. $-OS(O)_2CF_3$, $-OS(O)_2CH_3$, $-OS(O)_2PhMe$ or nonaflates), or an *N*-imidazolyl group and R^1 and Z are as hereinbefore defined, for example at around 0°C to room temperature, or at above room temperature (e.g. up to 40-180°C) in the presence of a suitable base (e.g. sodium hydride, sodium bicarbonate, potassium carbonate, pyrrolidinopyridine, pyridine, triethylamine,

tributylamine, trimethylamine, dimethylaminopyridine, diisopropylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium hydroxide, potassium hydroxide, *N*-ethyl-diisopropylamine, *N*-(methylpolystyrene)-4-(methylamino)pyridine, lithiumdiisopropylamide or mixtures thereof) and an appropriate solvent (e.g. tetrahydrofuran, pyridine, toluene, dichloromethane, chloroform, dimethylformamide, trifluoromethylbenzene, dimethylsulfoxide or triethylamine). Preferred base/solvent systems include sodium hydride/dimethylformamide, dimethylaminopyridine/pyridine, sodium hydroxide/dichloromethane (optionally in the presence of a phase transfer catalyst (e.g. tetrabutylammonium hydrogensulfate)), lithiumdiisopropylamide/tetrahydrofuran, potassium hydroxide/dimethyl-sulfoxide. Other systems that may be mentioned include sodium/ammonia.

(ii) reaction of a compound of formula IV,



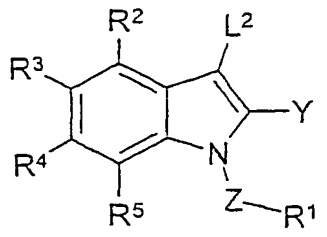
IV

wherein L^4 represents L^2 or L^3, in which L^2 represents a leaving group such as halo (e.g. chloro, bromo or iodo), a sulfonylate group (e.g. $-OS(O)_2CF_3$, $-OS(O)_2CH_3$, $-OS(O)_2PhMe$ or nonaflates) or $-B(OH)_2$, L^3 represents a leaving group such as $-B(OH)_2$, -4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl, $-SnBu_3$, or a similar group known to the skilled person, L^4 is attached to one or more of the carbon atoms of the benzenoid ring of the indole, and the remaining positions of the benzenoid ring are substituted with 1 to 3 (depending on the number of L^4 substituents) substituents R^2 to R^5 as appropriate, and Z, X, Y, R^1, R^2, R^3, R^4 and R^5 are as hereinbefore defined, with a compound of formula V,

$R^{22}L^5$ V

wherein R^{22} represents R^2, R^3, R^4 or R^5 (as appropriate), and L^5 represents L^2 (when L^4 is L^3) or L^3 (when L^4 is L^2) as hereinbefore defined. The skilled person will appreciate that L^2 and L^3 must be mutually compatible. This reaction may be performed, for example in the presence of a suitable catalyst system, e.g. a metal (or a salt or complex thereof) such as CuI, Pd/C, $Pd(OAc)_2$, $Pd(Ph_3P)_2Cl_2$, $Pd(Ph_3P)_4$, $Pd_2(dba)_3$ or $NiCl_2$ and a ligand such as *t*-Bu_3P, $(C_6H_{11})_3P$, Ph_3P, P(*o*-Tol)$_3$, 1,2-bis(diphenylphosphino)-ethane, 2,2'-bis(di-*tert*-butylphosphino)-1,1'-biphenyl, 2,2'-bis(diphenyl-phosphino)-1,1'-binaphthyl, 1,1'-bis(diphenylphosphinoferrocene), 1,3-bis(diphenylphosphino)propane or xantphos, together with a suitable base, such as Na_2CO_3, K_3PO_4, Cs_2CO_3, NaOH, K_2CO_3, CsF, Et_3N, (*i*-Pr)$_2$NEt or *t*-BuOK (or mixtures thereof) in a suitable solvent, such as dioxane, toluene, ethanol, dimethylformamide, ethylene glycol dimethyl ether, water, dimethylsulfoxide, acetonitrile, dimethylacetamide, *N*-methylpyrrolidinone or mixtures thereof. The reaction may also be carried out for example at room temperature or above (e.g. at a high temperature such as the reflux temperature of the solvent system) or using microwave irradiation;

(iii) for compounds of formula I, wherein X represents an optionally substituted aryl or heteroaryl group, reaction of a compound of formula VI,



VI

wherein Z, Y, L^2, R^1, R^2, R^3, R^4 and R^5 are as hereinbefore defined, with a compound of formula VII,

$$X^aL^3 \qquad \text{VII}$$

wherein X^a represents an aryl or heteroaryl group, optionally substituted as hereinbefore defined, and L^3 is as hereinbefore defined, for example under reaction conditions such as those hereinbefore described hereinbefore in respect of process step (ii);

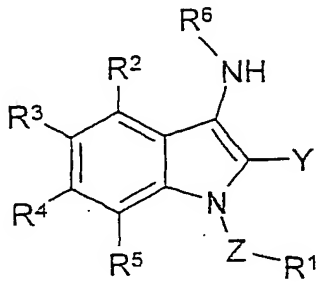
(iv) for compounds of formula I wherein X represents $-N(R^6)-E-R^7$, reaction of a compound of formula VI as hereinbefore defined, with a compound of formula VIII,

$$HN(R^6)-E-R^7 \qquad \text{VIII}$$

wherein E, R^6 and R^7 are as hereinbefore defined for example optionally in the presence of an appropriate metal catalyst (or a salt or complex thereof) such as Cu, $Cu(OAc)_2$, CuI (or CuI/diamine complex), $Pd(OAc)_2$, $Pd_2(dba)_3$ or $NiCl_2$ and an optional additive such as Ph_3P, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl or xantphos, in the presence of an appropriate base such as Et_3N, pyridine, *N,N'*-dimethylethylenediamine, Na_2CO_3, K_3PO_4, Cs_2CO_3 or *t*-BuOK (or mixtures thereof), in a suitable solvent (e.g. dichloromethane, dioxane, toluene, ethanol, dimethylformamide, ethylene glycol dimethyl ether, water, dimethylsulfoxide, acetonitrile, dimethylacetamide, *N*-methylpyrrolidinone or mixtures thereof) or in the absence of an additional solvent when the reagent may itself act as a solvent (e.g. when R^1 represents phenyl and L^1 represents bromo, i.e. bromobenzene). This reaction may be carried out at room temperature or above (e.g. at a high temperature, such as the reflux

temperature of the solvent system that is employed) or using microwave irradiation;

(v) for compounds of formula I wherein X represents -N(R^6)-E-R^7, reaction of a compound of formula IX,



IX

wherein Z, Y, R^1, R^2, R^3, R^4, R^5 and R^6 are as hereinbefore defined, with a compound of formula X,

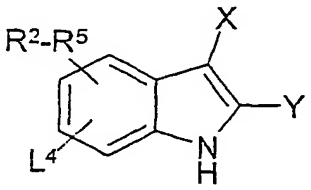
R^7-E-L^1 X

wherein E, R^7 and L^1 are as hereinbefore defined, for example under reaction conditions such as those hereinbefore described in respect of process step (i); or

(vi) for compounds of formula I wherein E represents a single bond and R^7 is a C_{1-6} alkyl group, C_{3-6} alkenyl or a C_{3-6} alkynyl group, reduction of a compound of formula I, wherein X represents –C(O)- and R^7 represents H, a C_{1-5} alkyl group, a C_{2-5} alkenyl or a C_{2-5} alkynyl group, in the presence of a suitable reducing agent. A suitable reducing agent may be an appropriate reagent that reduces the amide group to the amine group in the presence of other functional groups (for example an ester or a carboxylic acid). Suitable reducing agents include borane and other reagents known to the skilled person, under reaction conditions known to the skilled person.

Compounds of formula II may be prepared by:

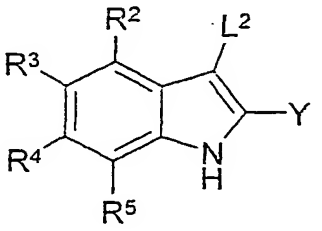
(a) reaction of a compound of formula XI,



XI

wherein X, Y, L^4, R^2, R^3, R^4 and R^5 are as hereinbefore defined with a compound of formula V for example under conditions such as those described hereinbefore in respect of process step (ii);

(b) for compounds of formula II wherein X represents an optionally substituted aryl or heteroaryl group, reaction of a compound of formula XII,



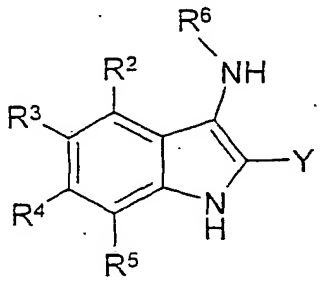
XII

wherein Y, L^2, R^2, R^3, R^4 and R^5 are as hereinbefore defined, with a compound of formula VII as hereinbefore defined, for example under conditions such as those described hereinbefore in respect of process step (iii);

(c) for compounds of formula II, wherein X represents $-N(R^6)-E-R^7$, reaction of a compound of formula XII as hereinbefore defined, with

a compound of formula VIII for example under conditions such as those described hereinbefore in respect of process step (iv);

(d) for compounds of formula II, wherein X represents $-N(R^6)-E-R^7$, reaction of a compound of formula XIII,



XIII

wherein Y, R^2, R^3, R^4, R^5 and R^6 are as hereinbefore defined with a compound of formula X for example under conditions such as those described hereinbefore in respect of process step (v);

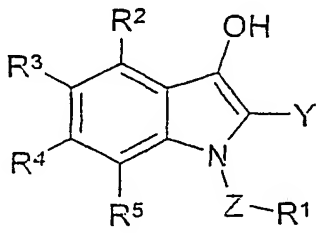
Compounds of formula IV may be prepared by reaction of a compound of formula XI as hereinbefore defined, with a compound of formula III as hereinbefore defined for example under conditions such as those described hereinbefore in respect of process step (i).

Compounds of formula IV in which L^4 represents L^3 may be prepared by reaction of a compound of formula IV in which L^4 represents L^2, with an appropriate reagent for the conversion of the L^2 group to the L^3 group. This conversion may be performed by methods known to those skilled in the art, for example, compounds of formula IV, in which L^3 is 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl may be prepared by reaction of the reagent bis(pinacolato)diboron with a compound of formula IV in which L^4 represents L^2, for example under reaction conditions such as those described hereinbefore in respect of process route (ii) above.

Compounds of formula VI may be prepared by:

(a) reaction of a compound of formula XII as hereinbefore defined with a compound of formula III as hereinbefore defined for example under conditions such as those described hereinbefore in respect of process step (i);

(b) for compounds of formula VI wherein L^2 represents a sulfonylate group, reaction of a compound of formula XIV,



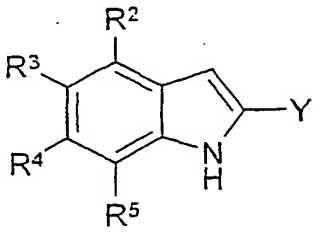
XIV

wherein Y, Z, R^1, R^2, R^3, R^4 and R^5 are as hereinbefore defined, with an appropriate reagent for the conversion of the hydroxyl group to the sulfonylate group (e.g. tosyl chloride, mesyl chloride, triflic anhydride and the like) under conditions known to those skilled in the art.

Compounds of formula IX may be prepared for example by reaction of a compound of formula XIII as hereinbefore defined with a compound of formula III as hereinbefore defined for example under conditions such as those described hereinbefore in respect of process step (i).

Compounds of formula XII may be prepared by standard techniques. For example:

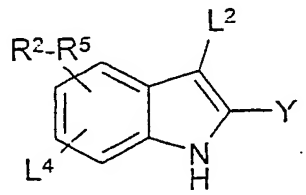
(a) Compounds of formula XII, wherein L^2 represents halo may be prepared by reaction of a compound of formula XV,



XV

wherein R^2, R^3, R^4, R^5 and Y are as hereinbefore defined, with a reagent, or mixture of reagents known to be a source of halide ions. For example, for bromide ions, *N*-bromosuccinimide may be employed, for iodide ions, iodine or a mixture of NaI and *N*-chlorosuccinimide may be employed, for chloride ions, *N*-chlorosuccinimide may be employed and for fluoride ions, 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) may be employed. This reaction may be carried out in a suitable solvent (e.g. acetone or benzene) under conditions known to the skilled person.

(b) by reaction of a compound of formula XVI,

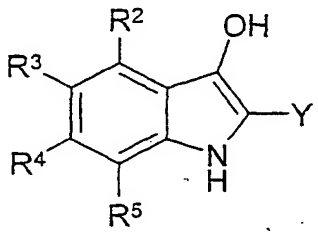


XVI

wherein Y, L^2, L^4, R^2, R^3, R^4 and R^5 are as hereinbefore defined with a compound of formula V as hereinbefore defined, for example

under reaction conditions such as those described hereinbefore in respect of process route (ii) above; or

(c) for compounds of formula XII wherein L^1 represents a sulfonylate group, reaction of a compound of formula XVII,



XVII

wherein Y, R^2, R^3, R^4 and R^5 are as hereinbefore defined, with an appropriate reagent for the conversion of the hydroxyl group to a sulfonylate group as described hereinbefore.

Compounds of formula XIII may be prepared by reaction of a compound of formula XII as hereinbefore defined with a compound of formula XVIII,

$$H_2NR^6 \qquad \text{XVIII}$$

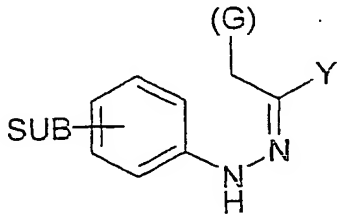
wherein R^6 is as hereinbefore defined, for example under reaction conditions such as those described in respect of process step (iv).

Compounds of formula XIII wherein R^6 represents hydrogen may be prepared by an aromatic nitration reaction carried out on a compound of formula XV, as hereinbefore defined, followed by reduction of the nitro group of the resultant intermediate to an amino group. Both reactions may be performed under conditions known to the skilled person.

Compounds of formulae III, V, VII, VIII, X, XVIII are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from available starting materials using appropriate reagents and reaction conditions.

Indoles of formulae II, IV, VI, IX, XI, XII, XIII, XIV, XV, XVI and XVII may also be prepared with reference to a standard heterocyclic chemistry textbook (e.g. "Heterocyclic Chemistry" by J. A. Joule, K. Mills and G. F. Smith, 3rd edition, published by Chapman & Hall) and/or made according to the following general procedures.

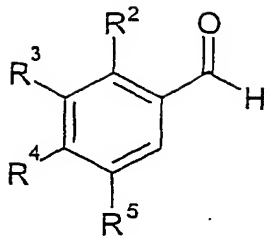
For example compounds of formulae II, XI, XIII and XV may be prepared by reaction of a compound of formula XIX,



XIX

wherein SUB represents the substitution pattern that is present in the compound of formula II, XI, XIII or XV to be formed, (G) represents either X (as required for formation of compounds of formulae II and XI), a $-N(R^6)H$ group (as required for formation of compounds of formula XIII) or the (G) substituent is absent (as required for formation of compounds of formula XV) and Y is as hereinbefore defined, under Fischer indole synthesis conditions known to the person skilled in the art.

Compounds of formula XV may alternatively be prepared by reaction of a compound of formula XX,



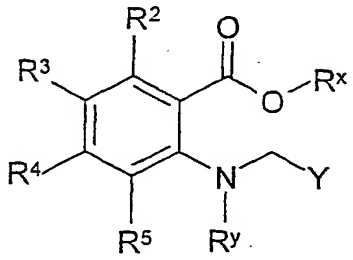
XX

wherein R^2, R^3, R^4 and R^5 are as hereinbefore defined with a compound of formula XXI,

$$N_3CH_2Y \qquad \text{XXI}$$

wherein Y is as hereinbefore defined, and preferably does not represent -COOH, under conditions known to the person skilled in the art (i.e. conditions to induce a condensation reaction, followed by a thermally induced cyclisation).

Compounds of formulae XIV and XVII may be prepared by reaction of a compound of formula XXII,

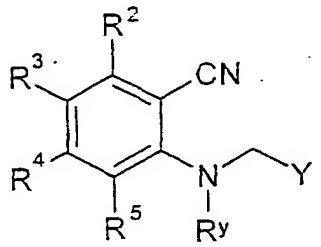


XXII

wherein R^x represents a C_{1-6} alkyl group, R^y represents either $-Z-R^1$ as hereinbefore defined (as required for formation of compounds of formula XIV), hydrogen (as required for formation of compounds of formula XVII) or a nitrogen-protected derivative thereof, and Y, R^2, R^3, R^4 and R^5 are as

hereinbefore defined, under standard cyclisation conditions known to those skilled in the art.

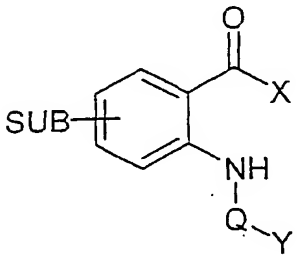
Compounds of formulae IX and XIII, wherein R^6 represents H, may be prepared by reaction of a compound of formula XXIII,



XXIII

wherein Y, R^2, R^3, R^4, R^5 and R^y are as hereinbefore defined, for example under intramolecular cyclisation conditions known to those skilled in the art.

Compounds of formula II and XI, wherein X represents aryl or heteroaryl, may alternatively be prepared by reaction of a compound of formula XXIV,



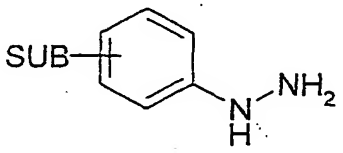
XXIV

wherein Q represents either –C(O)- or $–CH_2$-, X represents aryl or heteroaryl, and SUB and Y are as hereinbefore defined. When Q represents –C(O)-, the intramolecular cyclisation may be induced by a reducing agent such as $TiCl_3/C_8K$, $TiCl_4$/Zn or SmI_2 under conditions known to the skilled person, for example, at room temperature in the presence of a polar aprotic

solvent (such as THF). When Q represents $-CH_2-$, the reaction may be performed in the presence of base under intramolecular condensation reaction conditions known to the skilled person.

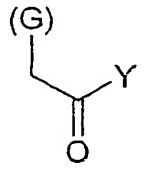
Compounds of formula XIX may be prepared by:

(a) reaction of a compound of formula XXV,



XXV

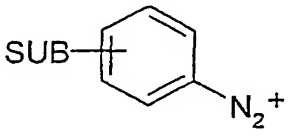
wherein SUB is as hereinbefore defined with a compound of formula XXVI,



XXVI

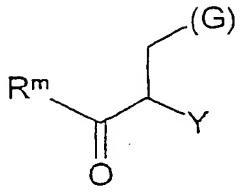
wherein (G) and Y are as hereinbefore defined under condensation conditions known to the skilled person; or

(b) reaction of a compound of formula XXVII,



XXVII

wherein SUB is as hereinbefore defined with a compound of formula XXVIII,



XXVIII

wherein R^m represents OH, O-C_{1-6} alkyl, C_{1-6} alkyl and (G) and Y are as hereinbefore defined, for example under Japp-Klingemann conditions known to the skilled person.

Compounds of formulae XX, XXI, XXII, XXIII, XIV, XV, XVI, XVII and XVIII are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from available starting materials using appropriate reagents and reaction conditions.

The substituents X, Y, Z, R^1, R^2, R^3, R^4 and R^5 in final compounds of the invention or relevant intermediates may be modified one or more times, after or during the processes described above by way of methods that are well known to those skilled in the art. Examples of such methods include substitutions, reductions, oxidations, alkylations, hydrolyses, esterifications, and etherifications. The precursor groups can be changed to a different such group, or to the groups defined in formula I, at any time during the reaction sequence. For example, in cases where Y represent a carboxylic acid ester functional group, the skilled person will appreciate that at any stage during the synthesis (e.g. the final step), the relevant substituent may be hydrolysed so forming for example a carboxylic acid functional group.

In cases where Y represents a carboxylic acid or carboxylic acid ester functional group, the relevant substituent may be reduced, under suitable conditions known to the skilled person (for example in the presence of other potentially reducible functional groups), at any stage during the synthesis (e.g. the final step), so forming for example a hydroxymethyl substituent.

Compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

It will be appreciated by those skilled in the art that, in the processes described above and hereinafter, the functional groups of intermediate compounds may need to be protected by protecting groups.

The protection and deprotection of functional groups may take place before or after a reaction in the above-mentioned schemes.

Protecting groups may be removed in accordance with techniques that are well known to those skilled in the art and as described hereinafter. For example, protected compounds/intermediates described herein may be converted chemically to unprotected compounds using standard deprotection techniques.

The type of chemistry involved will dictate the need, and type, of protecting groups as well as the sequence for accomplishing the synthesis.

The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by J W F McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

Medical and Pharmaceutical Uses

Compounds of the invention are indicated as pharmaceuticals. According to a further aspect of the invention there is provided a compound of the invention for use as a pharmaceutical.

Although compounds of the invention may possess pharmacological activity as such, certain pharmaceutically-acceptable (e.g. "protected") derivatives of compounds of the invention may exist or be prepared which may not possess such activity, but may be administered parenterally or orally and thereafter be metabolised in the body to form compounds of the invention. Such compounds (which may possess some pharmacological activity, provided that such activity is appreciably lower than that of the "active" compounds to which they are metabolised) may therefore be described as "prodrugs" of compounds of the invention.

By "prodrug of a compound of the invention", we include compounds that form a compound of the invention, in an experimentally-detectable amount, within a predetermined time (e.g. about 1 hour), following oral or parenteral administration. All prodrugs of the compounds of the invention are included within the scope of the invention.

Furthermore, certain compounds of the invention (including, but not limited to, compounds of formula I in which Y is $-C(O)OR^8$ and R^8 is other than hydrogen) may possess no or minimal pharmacological activity as such, but may be administered parenterally or orally, and thereafter be metabolised in the body to form compounds of the invention that possess pharmacological activity as such (including, but not limited to, corresponding compounds of formula I in which Y represents -COOH). Such compounds (which also includes compounds that may possess some pharmacological activity, but that

activity is appreciably lower than that of the "active" compounds of the invention to which they are metabolised), may also be described as "prodrugs".

Thus, the compounds of the invention are useful because they possess pharmacological activity, and/or are metabolised in the body following oral or parenteral administration to form compounds which possess pharmacological activity.

Compounds of the invention are particularly useful because they may inhibit (for example selectively) the activity of prostaglandin E synthases (mPGESs) and particularly the activity of microsomal prostaglandin E synthase-1 (mPGES-1), i.e. they prevent the action of mPGES-1 or a complex of which the mPGES-1 enzyme forms a part, and/or may elicit a mPGES-1 modulating effect, for example as may be demonstrated in the test described below. Compounds of the invention may thus be useful in the treatment of those conditions in which inhibition of a PGES, and particularly mPGES-1, is required.

Compounds of the invention are thus expected to be useful in the treatment of inflammation.

The term "inflammation" will be understood by those skilled in the art to include any condition characterised by a localised or a systemic protective response, which may be elicited by physical trauma, infection, chronic diseases, such as those mentioned hereinbefore, and/or chemical and/or physiological reactions to external stimuli (e.g. as part of an allergic response). Any such response, which may serve to destroy, dilute or sequester both the injurious agent and the injured tissue, may be manifest by, for example, heat, swelling, pain, redness, dilation of blood vessels

and/or increased blood flow, invasion of the affected area by white blood cells, loss of function and/or any other symptoms known to be associated with inflammatory conditions.

The term "inflammation" will thus also be understood to include any inflammatory disease, disorder or condition *per se*, any condition that has an inflammatory component associated with it, and/or any condition characterised by inflammation as a symptom, including *inter alia* acute, chronic, ulcerative, specific, allergic and necrotic inflammation, and other forms of inflammation known to those skilled in the art. The term thus also includes, for the purposes of this invention, inflammatory pain, pain generally and/or fever.

Accordingly, compounds of the invention may be useful in the treatment of inflammatory bowel disease, irritable bowel syndrome, migraine, headache, low back pain, fibromyalgia, myofascial disorders, viral infections (*e.g.* influenza, common cold, herpes zoster, and AIDS), bacterial infections, fungal infections, dysmenorrhea, burns, surgical or dental procedures, malignancies (*e.g.* breast cancer, colon cancer, and prostate cancer), atherosclerosis, gout, arthritis, osteoarthritis, juvenile arthritis, rheumatoid arthritis, rheumatic fever, ankylosing spondylitis, systemic lupus erythematosus, vasculitis, pancreatitis, nephritis, bursitis, conjunctivitis, iritis, scleritis, uveitis, wound healing, dermatitis, eczema, psoriasis, stroke, diabetes (e.g. diabetes mellitus), neurodegenerative disorders such as Alzheimer's disease and multiple sclerosis, autoimmune diseases, osteoporosis, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, allergic disorders, rhinitis, ulcers, coronary heart disease, sarcoidosis and any other disease with an inflammatory component.

Compounds of the invention are indicated both in the therapeutic and/or prophylactic treatment of the above-mentioned conditions.

According to a further aspect of the present invention, there is provided a method of treatment of a disease which is associated with, and/or which can be modulated by inhibition of, a PGES (such as a mPGES, e.g. mPGES-1), and/or a method of treatment of a disease in which inhibition of the activity of a PGES, and particularly mPGES-1, is desired and/or required (e.g. inflammation), which method comprises administration of a therapeutically effective amount of a compound of the invention, as hereinbefore defined, to a patient suffering from, or susceptible to, such a condition.

"Patients" include mammalian (including human) patients.

The term "effective amount" refers to an amount of a compound, which confers a therapeutic effect on the treated patient. The effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of or feels an effect).

Compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, sublingually, intraperitoneally, topically (e.g. ocularly), intramuscularly, intraspinally, epidurally, transdermally, by any other parenteral route or *via* inhalation, in a pharmaceutically acceptable dosage form.

Compounds of the invention may be administered alone, but are preferably administered by way of known pharmaceutical formulations, including tablets, capsules or elixirs for oral administration, suppositories for rectal

administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

Such formulations may be prepared in accordance with standard and/or accepted pharmaceutical practice.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Compounds of the invention may also be combined with other therapeutic agents that are useful in the treatment of inflammation (e.g. NSAIDs and coxibs).

According to a further aspect of the invention, there is provided a combination product comprising:

(A) a compound of the invention, as hereinbefore defined; and

(B) another therapeutic agent that is useful in the treatment of inflammation,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

Such combination products provide for the administration of a compound of the invention in conjunction with the other therapeutic agent, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises a compound of the invention, and at least one comprises the other therapeutic agent, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including a compound of the invention and the other therapeutic agent).

Thus, there is further provided:

(1) a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, another therapeutic agent that is useful in the treatment of inflammation, and a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(2) a kit of parts comprising components:

(a) a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including another therapeutic agent that is useful in the treatment of inflammation in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

Compounds of the invention may be administered at varying doses. Oral dosages may range from between about 0.01 mg/kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably about 0.01 to about 10 mg/kg/day, and more preferably about 0.1 to about 5.0 mg/kg/day. For oral administration, the compositions typically contain between about 0.01 mg to about 500 mg, and preferably between about 1 mg to about 100 mg, of the active ingredient. Intravenously, the most preferred doses will range from about 0.001 to about 10 mg/kg/hour during constant rate infusion. Advantageously, compounds may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily.

In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the route of administration, the type and severity of the condition that is to be treated, as well as the species, age, weight, sex, renal function, hepatic function and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of the invention may have the advantage that they are effective, and preferably selective, inhibitors of prostaglandin E synthases (PGES) and particularly microsomal prostaglandin E synthase-1 (mPGES-1). The compounds of the invention may reduce the formation of the specific arachidonic acid metabolite PGE_2 without reducing the formation of other arachidonic acid metabolites, and thus may not give rise to the associated side-effects mentioned hereinbefore.

Compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art, whether for use in the above-stated indications or otherwise.

Biological Test

In the assay mPGES-1 catalyses the reaction where the substrate PGH_2 is converted to PGE_2. mPGES-1 is expressed in *E. coli* and the membrane

fraction is dissolved in 20mM NaPi-buffer pH 8.0 and stored at -80 °C. In the assay mPGES-1 is dissolved in 0.1M KPi-buffer pH 7.35 with 2.5mM glutathione. The stop solution consists of H_2O / MeCN (7/3), containing $FeCl_2$ (25 mM) and HCl (0.15 M). The assay is performed at room temperature in 96-well plates. Analysis of the amount of PGE_2 is performed with reversed phase HPLC (Waters 2795 equipped with a 3.9 x 150 mm C18 column). The mobile phase consists of H_2O / MeCN (7/3), containing TFA (0.056%), and absorbance is measured at 195 nm with a Waters 2487 UV-detector.

The following is added chronologically to each well:

1. 100 µL mPGES-1 in KPi-buffer with glutathione. Total protein concentration: 0.02 mg/mL.
2. 1 µL inhibitor in DMSO. Incubation of the plate at room temperature for 25 minutes.
3. 4 µL of a 0.25mM PGH_2 solution. Incubation of the plate at room temperature for 60 seconds.
4. 100 µL stop solution.

180 µL per sample is analyzed with HPLC.

Examples

The invention is illustrated by way of the following examples, in which the following abbreviations may be employed:

BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
dba	dibenzylideneacetone
DMAP	4,4-dimethylaminopyridine
DME	ethylene glycol dimethyl ether
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate

HPLC	High Pressure Liquid Chromatography
MeCN	acetonitrile
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

Starting materials and chemical reagents specified in the syntheses described below are commercially available from, *e.g.* Sigma-Aldrich Fine Chemicals.

Example 1

6-(4-*tert*-Butylphenyl)-1-(3-phenoxybenzyl)-3-phenylindole-2-carboxylic acid

(a) 6-(4-*tert*-Butylphenyl)indole-2-carboxylic acid ethyl ester

A mixture of 6-bromoindole-2-carboxylic acid ethyl ester (400 mg, 1.5 mmol), 4-*tert*-butylphenylboronic acid (400 mg, 2.25 mmol), K_3PO_4 (950 mg, 1.5 mmol), $Pd(OAc)_2$ (18 mg, 0.075 mmol), 2,2'-bis(di-*tert*-butylphosphino)-1,1'-biphenyl (45 mg, 0.15 mmol), and toluene (9 mL) were stirred in an argon atmosphere for 30 min at room temperature, and at 100 °C for 40 min using microwave irradiation. The mixture was cooled to room temperature and poured into $NaHCO_3$ (aq., sat.). The mixture was extracted with EtOAc and the combined extracts were washed with water, brine and dried over Na_2SO_4. The organic phase was then concentrated and the product purified by chromatography to give the sub-title compound (392 mg, 81%).

(b) 6-(4-*tert*-Butylphenyl)-3-iodoindole-2-carboxylic acid ethyl ester

The reaction was performed with the exclusion of light. A solution of NaI (300 mg, 2.0 mmol) in acetone (15 mL) was added dropwise to a stirred solution of NCS (270 mg, 2.0 mmol) in acetone (4 mL), followed after 15 min by the dropwise addition of 6-(4-*tert*-butylphenyl)indole-2-carboxylic acid ethyl ester (650 mg, 2.0 mmol; see step (a) above) in acetone (20 mL). After 30 min at room temperature the mixture was poured into an aqueous solution of $Na_2S_2O_3$ (aq., 10%) and extracted with EtOAc. The combined extracts were washed with water, brine and dried over Na_2SO_4. The organic phase was then concentrated and then purified by chromatography to give the sub-title compound (743 mg, 82%).

(c) 6-(4-*tert*-Butylphenyl)-3-iodo-1-(3-phenoxybenzyl)-indole-2-carboxylic acid ethyl ester

A solution of 6-(4-*tert*-butylphenyl)-3-iodoindole-2-carboxylic acid ethyl ester (743 mg, 1.66 mmol; see step (b) above) in DMF (10 mL) was added carefully to a stirred suspension of NaH (41 mg, 1.69 mmol) in DMF (4 mL) at 0 °C. The mixture was stirred at room temperature for 25 min. A solution of 3-phenoxybenzyl chloride (378 mg, 1.69 mmol) in DMF (6 mL) was then added in portions and the mixture was stirred at room temperature for a further 24 h, then poured into water and extracted with *t*-BuOMe. The combined extracts were washed with water, brine and dried over Na_2SO_4. The organic phase was concentrated and the product purified by chromatography and then crystallisation from EtOH to give the sub-title compound (766 mg, 73%).

(d) 6-(4-*tert*-Butylphenyl)-1-(3-phenoxybenzyl)-3-phenylindole-2-carboxylic acid ethyl ester

A mixture of 6-(4-*tert*-butylphenyl)-3-iodo-1-(3-phenoxybenzyl)-indole-2-carboxylic acid ethyl ester (200 mg, 0.32 mmol; see step (c) above),

phenylboronic acid (59 mg, 0.48 mmol), K_3PO_4 (238 mg, 1.12 mmol), $Pd(OAc)_2$ (3.6 mg, 0.016 mmol) and toluene (3 mL) was stirred for 20 min at room temperature and then for 4 h at 80 °C. The mixture was poured into $NaHCO_3$ (aq., sat.) and extracted with EtOAc. The combined extracts were washed with water, brine and dried over Na_2SO_4. The organic phase was then concentrated and the product purified by column chromatography to give the sub-title compound (163 mg, 88%).

(e) 6-(4-*tert*-Butylphenyl)-1-(3-phenoxybenzyl)-3-phenylindole-2-carboxylic acid

A mixture of 6-(4-*tert*-butylphenyl)-1-(3-phenoxybenzyl)-3-phenylindole-2-carboxylic acid ethyl ester (163 mg, 0.281 mmol; see step (d)), aqueous NaOH (1 M, 10 mL) and MeCN (40 mL) was heated at reflux for 4 h. The mixture was then allowed to cool, acidified with HCl (1M) to pH 2 and extracted with EtOAc. The combined extracts were washed with water, brine and dried over Na_2SO_4. The combined extracts were concentrated and the product was purified by chromatography and recrystallisation firstly from EtOH and then from MeCN to give the title compound (95 mg, 61%).

^{1}H NMR (DMSO-d_6, 200 MHz): δ 7.61-7.37 (12H, m), 7.29-7.17 (3H, m), 7.09-7.00 (1H, m), 6.97-6.90 (2H, m), 6.85 (1H, d, *J*=2.0 Hz), 6.83-6.77 (2H, m), 5.86 (2H, s), 1.37 (9H, s).

Example 2

6-(4-*tert*-Butylphenyl)-1-(3-phenoxybenzyl)-3-(2-thienyl)indole-2-carboxylic acid

(a) 6-(4-*tert*-Butylphenyl)-1-(3-phenoxybenzyl)-3-(2-thienyl)indole-2-carboxylic acid ethyl ester

2-(Tributylstannyl)thiophene (72 mg, 0.20 mmol) was added to a stirred mixture of 6-(4-*tert*-butylphenyl)-3-iodo-1-(3-phenoxybenzyl)-indole-2-

carboxylic acid ethyl ester (150 mg, 0.24 mmol; see Example 1(d)), CuI (25 mg, 0.13 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.026 mmol) and DMF (3 mL). After 10 min at room temperature and 1 h at 90°C another portion of 2-(tributylstannyl)thiophene (72 mg, 0.20 mmol) was added and the heating was continued for 3 h. The mixture was filtered through Celite® and the solids were washed with EtOAc. Concentration and purification by chromatography gave the sub-title compound (125 mg, 90%).

(b) 6-(4-*tert*-Butylphenyl)-1-(3-phenoxybenzyl)-3-(2-thienyl)indole-2-carboxylic acid ethyl ester

A mixture of 6-(4-*tert*-butylphenyl)-1-(3-phenoxybenzyl)-3-phenylindole-2-carboxylic acid ethyl ester (125 mg, 0.213 mmol; see step (a)), aqueous KOH (2M, 2 mL) and MeCN (6 mL) was heated for 30 min at 130°C using microwave irradiation. The mixture was acidified with HCl (1M) to pH 2 and extracted with EtOAc. The combined extracts were washed with water, brine and dried over Na_2SO_4. Concentration and purification by chromatography gave the title compound (91 mg, 77%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 7.75 (1H, d, *J*=8.4 Hz), 7.56-7.45 (6H, m), 7.44 (1H, dd, *J*=4.0, 1.4 Hz), 7.30-7.15 (5H, m), 7.09-7.03 (1H, m), 6.98-6.90 (2H, m), 6.86-6.79 (3H, m), 5.86 (2H, s), 1.37 (9H, s).

Example 3

5-(3,4-Methylenedioxyphenyl)-3-phenyl-1-(3-phenylpropyl)indole-2-carboxylic acid

(a) *N*-(2-Benzoyl-4-chlorophenyl)oxalamic acid ethyl ester

A mixture of 2-amino-5-chlorobenzophenone (11.6 g, 50 mmol), ethyl oxalyl-chloride (6.8 g, 50 mmol) and toluene (70 mL) was heated at reflux for 1.5 h. On cooling a yellow precipitate formed. EtOAc (250 mL) was added and the

solution was washed with $NaHCO_3$ (aq., 5%), H_3PO_4 (aq., 5%), brine and dried over Na_2SO_4. Concentration gave the sub-title compound (15.5g, 94%).

(b) 5-Chloro-3-phenylindole-2-carboxylic acid ethyl ester

$TiCl_4$ in THF (0.25 M, 19.5 mL, 54.9 mmol) was added slowly to a stirred mixture of *N*-(2-benzoyl-4-chlorophenyl)oxalamic acid ethyl ester (8.88 g, 26.8 mmol; see step (a)), Zn (7.19 g, 110 mmol) and THF (60 mL) at room temperature. After 2 h, silica gel was added and then after a further 30 min the mixture was filtered through a pad of silica gel which was washed with EtOAc. The combined filtrates were washed with $NaHCO_3$ (aq., 5%), water, brine and dried over Na_2SO_4. Concentration and crystallisation of the residue from CH_2Cl_2/petroleum ether gave the title compound (3.13g, 39%).

(c) 5-Chloro-3-phenyl-1-(3-phenylpropyl)indole-2-carboxylic acid ethyl ester

NaH (60 % dispersion in mineral oil, 0.25 g, 6.2 mmol) was washed with hexane (2x1 mL) and Et_2O (1 mL) and suspended in DMF (1 mL). A solution of 5-chloro-3-phenylindole-2-carboxylic acid ethyl ester (1.55 g, 5.17 mmol; see step (b)) in DMF (10 mL) was added carefully at 0°C and the mixture was stirred for 20 min. A solution of (3-bromopropyl)-benzene (1.54 g, 7.75 mmol) in DMF (3mL) was added carefully at 0°C. The cooling bath was removed and the mixture was stirred at room temperature for 16 h, poured into water, and extracted with EtOAc. The extract was washed with water, brine and dried over Na_2SO_4. Concentration and chromatography gave the title compound (1.66 g, 77%).

(d) 5-(3,4-Methylenedioxyphenyl)-3-phenyl-1-(3-phenylpropyl)indole-2-carboxylic acid

The title compound was prepared in accordance with the procedure in Example 1(a) from 5-chloro-3-phenyl-1-(3-phenylpropyl)indole-2-carboxylic acid ethyl ester (see step (c)) and 3,4-

methylenedioxyphenylboronic acid, followed by hydrolysis in accordance with the procedure described in Example 2(b).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.61-7.38 (8H, m), 7.36-7.15 (5H, m), 7.04 (1H, s), 7.02 (1H, dd, *J*=8.5, 1.8 Hz), 6.85 (1H, d, *J*=8.5 Hz), 5.98 (2H, s), 4.67-4.55 (2H, m), 2.75 (2H, t, *J*=7.6 Hz), 2.31-2.12 (2H, m).

Example 4

3-Phenyl-1-(3-phenylpropyl)-5-(3-pyridyl)indole-2-carboxylic acid

(a) 3-Phenyl-1-(3-phenylpropyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole-2-carboxylic acid ethyl ester

A 0.01 M stock solution of a $Pd/(C_6H_{11})_3P$ was prepared from $Pd_2(dba)_3$, (0.457 g, 0.5 mmol), tricyclohexylphosphine (0.841 g, 3 mmol) and dioxane (100 mL). An aliquot of this stock solution (12.5 mL, 0.125 mmol Pd), 5-chloro-3-phenyl-1-(3-phenylpropyl)indole-2-carboxylic acid ethyl ester (1.05 g, 2.5 mmol; see Example 3(c)), bis(pinacolato)diboron (0.762 g, 3.0 mmol), KOAc (0.44 g, 4.5 mmol), and dioxane (25 mL) were heated at 80°C for 16 h. Another aliquot of the $Pd/(C_6H_{11})_3P$ reagent (2.5 mL, 0.025 mmol Pd) was added and the mixture was heated at 100°C for 24 h. The mixture was filtered through Celite®, and the filtrate was concentrated and purified by chromatography to give the sub-title compound (0.47 g, 37 %) together with 0.55 g recovered starting material.

(b) 3-Phenyl-1-(3-phenylpropyl)-5-(3-pyridyl)indole-2-carboxylic acid ethyl ester

3-Phenyl-1-(3-phenylpropyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole-2-carboxylic acid ethyl ester (0.40 g, 91 mmol; see step (a)), 3-iodopyridine (0.28 g, 1.37 mmol), aqueous Na_2CO_3 (2M, 0.46 mL, 0.91 mmol), $Pd(PPh_3)_4$ (53 mg, 46 μmol), toluene (7.3 mL), and EtOH (1.8 mL) were heated at 80°C for 16 h. More 3-iodopyridine (0.19 g, 0.91 mmol),

aqueous Na_2CO_3 (2M, 1.4 mL, 2.73 mmol), and $Pd(PPh_3)_4$ (23 mg, 20 μmol) were added and the mixture was heated for a further 8 h. EtOAc (30 mL) and brine (30 mL) were added. The layers were separated and the aqueous phase was washed with EtOAc. The combined organic phases were dried with brine and Na_2SO_4. Concentration and chromatography gave the sub-title compound (0.32 g, 76%).

(c) 3-Phenyl-1-(3-phenylpropyl)-5-(3-pyridyl)indole-2-carboxylic acid

The title compound was prepared from 3-phenyl-1-(3-phenylpropyl)-5-(3-pyridyl)indole-2-carboxylic acid ethyl ester (see step (b)) in accordance with the procedure in Example 2(b).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.78 (1H, s), 8.52 (1H, d, *J*=4.2 Hz), 7.92 (1H, d, *J*=8.0 Hz)), 7.65-7.71 (1H, m), 7.59-7.13 (13H, m), 4.71-4.58 (2H, m), 2.75 (2H, t, *J*=7.6 Hz), 2.32-2.17 (2H, m).

Example 5

6-(4-Benzyloxyphenyl)-3-(3-carboxyphenyl)-1-(3-nitrobenzyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1 from 4-benzyloxyphenylboronic acid, 3-nitrobenzylbromide and 3-carboxyphenylboronic acid.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 13.02 (2H, s), 8.13-7.94 (5H, m), 7.75 (1H, ddd, *J*=7.6, 1.5, 1.5 Hz), 7.63 (1H, dd, *J*=7.6, 2.0 Hz), 7.59-7.27 (12H, m), 7.04-6.97 (1H, m), 6.12 (2H, s), 5.18 (2H, s).

Example 6

3-(3-Carboxyphenyl)-4-phenyl-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1 from 4-bromoindole-2-carboxylic acid ethyl ester, phenylboronic acid, 3-(trifluoromethyl)benzylbromide and 3-carboxyphenylboronic acid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.79 (1H, dd, *J*=1.5, 1.5 Hz), 7.70 (1H, ddd, *J*=7.7, 1.5, 1.5 Hz), 7.57-7.50 (2H, m), 7.47-7.34 (3H, m), 7.25-7.20 (1H, m), 7.06 (1H, dd, *J*=6.2, 1.8 Hz), 7.06-6.85 (7H, m), 5.93 (2H, s).

Example 7

6-(4-Benzyloxyphenyl)-1-(3-nitrobenzyl)-3-(2-oxopyrrolidin-1-yl)indole-2-carboxylic acid

(a) 6-(4-Benzyloxyphenyl)-1-(3-nitrobenzyl)-3-(2-oxopyrrolidin-1-yl)indole-2-carboxylic acid ethyl ester

A stock suspension of a CuI/$MeNHCH_2CH_2NHMe$ complex was prepared by heating CuI (95.2 mg, 0.5 mmol), $MeNHCH_2CH_2NHMe$ (213μL, 2.0 mmol), and dioxane (5 mL) at 100°C for 5 min using microwave irradiation. 1.5 mL of this solution was added to 6-(4-benzyloxyphenyl)-3-iodo-1-(3-nitrobenzyl)indole-2-carboxylic acid ethyl ester (630 mg, 1.0 mmol, prepared in accordance with Example 1 from 6-bromoindole-2-carboxylic acid ethyl ester, 4-benzyloxyphenylboronic acid, and 3-nitrobenzylbromide), K_3PO_4 (530 mg, 2.5 mmol), and dioxane (5 mL). Pyrrolidinone (390 mg, 5.0 mmol) was added and the mixture was stirred at 95°C for 24 h, cooled to room temperature, poured into aqueous HCl (0.1M) and extracted with EtOAc. The combined extracts were dried with brine and Na_2SO_4. Concentration and chromatography gave the sub-title compound (538 mg, 91%).

(b) 6-(4-Benzyloxyphenyl)-1-(3-nitrobenzyl)-3-(2-oxopyrrolidin-1-yl)indole-2-carboxylic acid

6-(4-Benzyloxyphenyl)-1-(3-nitrobenzyl)-3-(2-oxopyrrolidin-1-yl)indole-2-carboxylic acid ethyl ester (see step (a)) was hydrolyzed in accordance with Example 2(b), using dioxane as the solvent, to give the title compound.

^{1}H NMR (DMSO, 200 MHz): δ 13.37 (1H, s), 8.10-8.06 (2H, m), 7.96 (1H, s), 7.66-7.26 (12H, m), 7.00 (1H, d, *J*=7.8 Hz), 6.06 (2H, s), 5.17 (2H, s), 3.81-3.74 (2H, m), 2.46-2.38 (2H, m), 2.24-2.06 (2H, m).

Example 8

3-(2-Oxopyrrolidin-1-yl)-1-(3-phenoxybenzyl)-5-phenylindole-2-carboxylic acid

The title compound was prepared in accordance with Example 7 from 5-bromoindole-2-carboxylic acid ethyl ester, phenylboronic acid, 3-phenoxybenzylchloride and pyrrolidinone.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.69-7.65 (1H, m), 7.63-7.52 (3H, m), 7.50-7.15 (7H, m), 7.13-7.01 (1H, m), 7.00-6.91 (2H, m), 6.88-6.79 (3H, m), 5.74 (2H, s), 3.98 (2H, t, *J*=7.0 Hz), 2.72 (2H, t, *J*=8.0 Hz), 2.41-2.34 (2H, m).

Example 9

1-(3,5-Difluorobenzyl)-4-methoxy-3-(2-oxopyrrolidin-1-yl)-7-phenyl-indole-2-carboxylic acid

(a) 2-Azido-3-(4-methoxybiphenyl-3-yl)acrylic acid ethyl ester

A solution of 4-methoxybiphenyl-3-carboxaldehyde (1.8 g, 8.48 mmol) and azidoacetic acid ethyl ester (5.62 g, 44 mmol) in EtOH (15 mL) was added dropwise to a solution of NaOEt (3.13 g, 46 mmol) in EtOH (35 mL) at -25°C. The mixture was stirred at that temperature for 10 min, kept in the freezer (-18°C) for 24 h and then poured whilst stirring vigorously to a cooled (0°C) solution of NH_4Cl (aq., sat.). The mixture was extracted with EtOAc

and the combined extracts were washed with brine and dried over Na_2SO_4. Concentration and crystallisation from EtOH gave the title compound (1.80 g, 66%).

(b) 4-Methoxy-7-phenylindole-2-carboxylic acid ethyl ester

A solution of 2-azido-3-(4-methoxybiphenyl-3-yl)acrylic acid ethyl ester (1.75 g, 5.40 mmol; see step (a)) in *o*-xylene (25 mL) was added dropwise to boiling *o*-xylene (25 mL). The heating was continued for 5 min, then the solution was allowed to cool to room temperature and kept in the freezer (-18°C) for 16 h. The precipitate was isolated by filtration, washed with petroleum ether and dried *in vacuo* to afford the sub-title compound (1.20 g, 74%).

(c) 1-(3,5-Difluorobenzyl)-4-methoxy-3-(2-oxopyrrolidin-1-yl)-7-phenyl-indole-2-carboxylic acid

The title compound was prepared from 4-methoxy-7-phenylindole-2-carboxylic acid ethyl ester (see step (b)) in accordance with Example 7.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 7.34-7.21 (3H, m), 7.10-7.06 (2H, m), 7.01-6.91 (1H, m), 6.94 (1H, d, *J*=7.8 Hz), 6.67 (1H, d, *J*=8.1 Hz), 5.92-5.89 (2H, m), 5.51-5.28 (2H, m), 3.89 (3H, s), 3.77-3.67 (2H, m), 2.37-2.17 (2H, m), 2.14-2.10 (2H, m).

Example 10

6-(3,4-Methylenedioxyphenyl)-1-[3,5-bis(trifluoromethyl)benzyl]-3-(4-chlorobenzoylamino)indole-2-carboxylic acid

The title compound was prepared according in accordance with Example 7 from 6-bromoindole-2-carboxylic acid ethyl ester, 3,4-methylenedioxyphenylboronic acid, 3,5-bis(trifluoromethyl)benzylchloride and 4-chlorobenzamide.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 10.35 (1H, s), 8.09-8.03 (2H, m), 8.01-7.99 (1H, m), 7.95-7.94 (1H, m), 7.81 (2H, s), 7.73 (1H, d, *J*=8.6 Hz), 7.66-7.59 (2H, m), 7.44 (1H, dd, *J*=8.6, 1.2 Hz), 7.34 (1H, d, *J*=1.8 Hz), 7.22 (1H, dd, *J*=8.2, 1.8 Hz), 6.99 (1H, d, *J*=8.2 Hz), 6.08 (2H, s), 6.05 (2H, s).

Example 11

3-(3,5-Dimethoxybenzoylamino)-5-(4-nitrophenyl)-1-(3-phenoxy-benzyl)indole-2-carboxylic acid

The title compound was prepared from 5-(4-nitrophenyl)indole-2-carboxylic acid ethyl ester (prepared from 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole-2-carboxylic acid ethyl ester (prepared from 5-bromoindole-2-carboxylic acid ethyl ester) and 4-nitrobromobenzene), 3-phenoxy-benzylchloride and 3,5-dimethoxybenzamide in accordance with Example 7.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 10.37 (1H, s), 8.32-8.24 (2H, m), 8.15 (1H, s), 8.01-7.91 (2H, m), 7.76 (2H, s), 7.41-7.16 (5H, m), 7.15-7.05 (1H, m), 6.99-6.90 (2H, m), 6.84-6.69 (4H, m), 5.90 (2H, s), 3.81 (6H, s).

Example 12

3-(3-Amino-4-methylbenzoylamino)-5-(4-*tert*-butylphenyl)-1-(3-chloro-benzyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 7 from 5-bromoindole-2-carboxylic acid ethyl ester, 4-*tert*-butylphenylboronic acid, 3-chlorobenzylchloride and 3-amino-4-methylbenzamide.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 10.09 (1H, s), 8.00 (1H, s), 7.69-7.40 (6H, m), 7.36-7.31 (3H, m), 7.19-6.94 (3H, m), 5.86 (2H, s), 4.3 (1H, br s), 3.3 (1H, br s), 2.11 (3H, s), 1.29 (9H, s).

Example 13

5-(4-*tert*-Butylphenyl)-1-(3-chlorobenzyl)-3-[(pyridine-3-carbonyl)amino]-indole-2-carboxylic acid

The title compound was prepared in accordance with Example 7 from 5-bromoindole-2-carboxylic acid ethyl ester, 4-*tert*-butylphenylboronic acid, 3-chlorobenzylchloride and nicotinamide.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 10.50 (1H, s), 9.20 (1H, s), 8.80-8.71 (1H, m), 8.42-8.31 (1H, m), 7.91 (1H, s), 7.32-7.52 (5H, m), 7.48-7.40 (2H, m), 7.34-7.27 (2H, m), 7.14 (1H, s), 7.06-6.97 (1H, m), 5.89 (2H, s), 1.29 (9H, s).

Example 14

3-[4-(Dimethylamino)butyrylamino]-6-(3.4-methylenedioxyphenyl)-1-(3-phenoxybenzyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 7 from 6-bromoindole-2-carboxylic acid ethyl ester, 3,4-methylenedioxyphenylboronic acid, 3-phenoxybenzylchloride and 4-(dimethylamino)-butyrylamide.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 12.3-11.2 (1H, br s), 8.22 (1H, d, J=8.6 Hz), 7.54 (1H, s), 7.37-7.05 (7H, m), 7.00-6.84 (5H, m), 6.71 (1H, dd, J=8.2, 2.3 Hz), 6.14 (2H, s), 6.07 (2H, s), 2.81 (2H, t, J=7.5 Hz), 2.54 (6H, s), 2.46 (2H, t, J=7.3 Hz), 1.94 (2H, dt, J=7.5, 7.3 Hz).

Example 15

1-(3-Cyanobenzyl)-6-(3.4-methylenedioxyphenyl)-3-(3-phenylacryloyl-amino)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 7 from 6-bromoindole-2-carboxylic acid ethyl ester, 3,4-methylenedioxyphenylboronic acid, 3-cyanobenzylchloride and cinnamamide.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 11.95 (1H, br s), 8.28 (1H, d, J=8.6 Hz), 7.70-7.59 (6H, m), 7.54-7.37 (6H, m), 7.28-7.23 (2H, m), 7.15 (1H, dd,

J=8.2, 1.8 Hz), 6.96 (1H, d, J=8.2 Hz), 6.88 (1H, d, J=15.8 Hz), 6.16 (2H, s), 6.03 (2H, s).

Example 16

1-(3-Carbamoylbenzyl)-6-(3.4-methylenedioxyphenyl)-3-(3-phenylacryloyl-amino)indole-2-carboxylic acid

The title compound was isolated in the last synthetic step (the hydrolysis) in the preparation of the title compound of Example 15.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 11.58 (1H, br s), 8.17 (1H, d, J=8.6 Hz), 7.89 (1H, s), 7.74-7.55 (6H, m), 7.48-7.37 (3H, m), 7.34-7.23 (4H, m), 7.16-7.08 (2H, m), 6.95 (1H, d, J=8.2 Hz), 6.91 (1H, d, J=15.6 Hz), 6.13 (2H, s), 6.03 (2H, s).

Example 17

3-Acetylamino-5-(3.4-methylenedioxyphenyl)-1-(5-phenoxypentyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 7 from 5-bromoindole-2-carboxylic acid ethyl ester, 3,4-methylenedioxy-phenylboronic acid, (5-bromopentyloxy)benzene, and acetamide.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 9.60 (1H, s), 7.71 (1H, s), 7.65-7.49 (2H, m), 7.30-7.15 (3H, m), 7.09 (1H, dd, J=8.1, 1.4 Hz), 6.77 (1H, d, J=8.1 Hz), 6.93-6.82 (3H, m), 6.04 (2H, s), 4.60-4.46 (2H, m), 3.90 (2H, t, J=6.3 Hz), 2.09 (3H, s), 1.81-1.61 (4H, m), 1.48-1.32 (2H, m).

Example 18

5-(3.4-Methylenedioxyphenyl)-3-(2-oxopiperidin-1-yl)-1-(5-phenoxy-pentyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 7 from 5-bromoindole-2-carboxylic acid ethyl ester, 3,4-methylenedioxy-phenylboronic acid, (5-bromopentyloxy)benzene, and 2-piperidone.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 7.66-7.49 (3H, m), 7.30-7.18 (3H, m), 7.13 (1H, dd, *J*=8.1, 1.8 Hz), 6.97 (1H, d, *J*=8.1 Hz), 6.92-6.83 (3H, m), 6.04 (2H, s), 4.65-4.50 (2H, m), 3.91 (2H, t, *J*=6.4 Hz), 3.64-3.55 (2H, m), 2.44-2.28 (2H, m), 1.98-1.64 (8H, m), 1.52-1.33 (2H, m).

Example 19

3-(3-Acetylphenyl)-5-(4-methoxyphenyl)-1-[3-(trifluoromethyl)benzyl]-indole-2-carboxylic acid

(a) 5-(4-Methoxyphenyl)indole-2-carboxylic acid ethyl ester

A mixture of 5-bromoindole-2-carboxylic acid ethyl ester (268 mg, 1.0 mmol), 4-methoxyphenylboronic acid (243 mg, 1.6 mmol), $Pd(OAc)_2$ (11.2 mg, 50 nmol), 2-(di-*t*-butylphosphino)biphenyl (60 mg, 200 nmol), K_3PO_4 (425 mg, 2 mmol) and toluene (2 mL) was heated at 170°C for 10 min using microwave irradiation. The mixture was extracted with EOAc, and the combined extracts washed with water, dried with Na_2SO_4, and concentrated. The residue was crystallised from EtOH to yield the sub-title compound (50%).

(b) 3-Iodo-5-(4-methoxyphenyl)indole-2-carboxylic acid ethyl ester

NaI (566 mg, 3.8 mmol) in acetone (18 mL) was added dropwise to a solution of NCS (458.5 mg, 3.4 mmol) in acetone (6 mL) at room temperature. After 15 min, 5-(4-methoxyphenyl)indole-2-carboxylic acid ethyl ester (1.01 g, 3.4 mmol; see step (a)) in acetone (48 mL) was added. After 60 min $Na_2S_2O_3$ (aq., 10%) was added and the mixture was extracted with EtOAc, and the combined extracts washed with water, dried with Na_2SO_4, and concentrated. The residue was crystallised from EtOAc/heptane to yield the sub-title compound (958 mg, 66%)

(c) 3-Iodo-5-(4-methoxyphenyl)-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid ethyl ester

A mixture of 3-iodo-5-(4-methoxyphenyl)indole-2-carboxylic acid ethyl ester (200 mg, 475 nmol; see step (b)), 1-(bromomethyl)-3-(trifluoromethyl)benzene (182 µL, 1.2 mmol), NaH (48 mg, 2 mmol) and DMF (2.5 mL) was heated at 170°C for 2 min using microwave irradiation. The mixture was extracted with EOAc. The combined extracts were washed with water, dried with Na_2SO_4 and concentrated. The residue was crystallised from EtOH to yield the sub-title compound (several batches were combined and employed in subsequent steps).

(d) 3-(3-Acetylphenyl)-5-(4-methoxyphenyl)-1-[3-(trifluoromethyl)benzyl]-indole-2-carboxylic acid ethyl ester

A mixture of 3-iodo-5-(4-methoxyphenyl)-1-[3-(trifluoromethyl)benzyl]-indole-2-carboxylic acid ethyl ester (100 mg, 173 nmol; see step (c)), 3-acetylphenylboronic acid (42.5 mg, 259 nmol), Na_2CO_3 (27 mg, 259 nmol), $Pd(PPh_3)_2Cl_2$ (6.1 mg, 9 nmol) and DME/H_2O/EtOH 7:3:2 (1 mL) was heated at 160°C for 10 minutes using microwave irradiation. The reaction mixture was filtered through Celite® and the filter cake was washed with Et_2O. The combined filtrates were poured into $NaHCO_3$ (aq., sat.) and extracted with Et_2O. The combined extracts were dried over Na_2SO_4 and concentrated. Purification by chromatography yielded the sub-title compound (74 mg, 71%).

(e) 3-(3-Acetylphenyl)-5-(4-methoxyphenyl)-1-[3-(trifluoromethyl)benzyl]-indole-2-carboxylic acid

A mixture of 3-(3-acetylphenyl)-5-(4-methoxyphenyl)-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid ethyl ester (59 mg, 103 nmol; see step (d)), NaOH (2 M, 500 µL) and MeCN (2 mL) was heated at 120°C for 10 min using microwave irradiation. The mixture was acidified with HCl

(2M) and extracted with EOAc. The combined extracts were dried and concentrated. Purification by chromatography yielded the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.10 (m, 1H), 7.99 (m, 1H), 7.71 (m, 1H), 7.63-7.54 (m, 3H), 7.53-7.47 (m, 3H), 7.46 (m, 1H), 7.40 (m, 1H), 7.35 (d, *J*=8 Hz, 1H), 7.18 (d, *J*=8 Hz, 1H), 6.94 (m, 2H), 5.88 (s, 2H), 3.83 (s, 3H), 2.61 (s, 3H).

Example 20

5-(4-Methoxyphenyl)-3-phenyl-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid

(a) 5-(4-Methoxyphenyl)-3-phenyl-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid ethyl ester

A mixture of 3-iodo-5-(4-methoxyphenyl)-1-[3-(trifluoromethyl)benzyl]-indole-2-carboxylic acid ethyl ester (12.9 mg, 22 nmol; see Example 19(c)), phenylboronic acid (4.1 mg, 33 nmol), K_3PO_4 (17 mg, 78 nmol), $Pd(OAc)_2$ (0.25 mg, 1.0 nmol) and toluene (500 μL) was heated at 170°C for 5 minutes using microwave irradiation. The mixture was filtered through Celite® and the filter cake was washed with Et_2O. The combined filtrates were poured into $NaHCO_3$ (aq., sat.) and extracted with Et_2O. The combined extracts were dried over Na_2SO_4 and concentrated. Purification by chromatography yielded the sub-title compound (60%).

(b) 5-(4-Methoxyphenyl)-3-phenyl-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid

The title compound was prepared from 5-(4-methoxyphenyl)-3-phenyl-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid ethyl ester (see step (a)) in accordance with Example 19(e).

Example 21

3,5-Bis(4-methoxyphenyl)-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid

The title compound was prepared in accordance with Example 20 using 4-methoxyphenylboronic acid instead of phenylboronic acid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.68 (m, 1H), 7.59 (dd, *J*=9, 2 Hz, 1H), 7.52-7.46 (m, 5H), 7.45 (m, 1H), 7.40-7.34 (m, 2H), 7.19 (d, *J*=7 Hz, 1H), 7.02 (m, 2H), 6.95 (m, 2H), 5.87 (s, 2H), 3.89 (s, 3H), 3.84 (s, 3H).

Example 22

5-(4-Methoxyphenyl)-3-(3-nitrophenyl)-1-[3-(trifluoromethyl)benzyl]-indole-2-carboxylic acid

The title compound was prepared in accordance with Example 19 using 3-nitrophenylboronic acid and 2.5 mol% $Pd(PPh_3)_2Cl_2$.

^{1}H NMR (200 MHz, $CDCl_3$): δ 8.39 (m, 1H), 8.26 (m, 1H), 7.83 (m, 1H), 7.65 (m, 1H), 7.62 (m, 1H), 7.58 (m, 1H), 7.54-7.34 (m, 6H), 7.19 (d, *J*=7 Hz, 1H), 6.95 (m, 2H), 5.89 (s, 2H), 3.83 (s, 3H).

Example 23

5-(4-Methoxyphenyl)-3-(pyridin-3-yl)-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid

The title compound was prepared in accordance with Example 19 using pyridin-3-ylboronic acid and 5 mol% $Pd(PPh_3)_2Cl_2$.

^{1}H NMR (200 MHz, DMSO-d_6): δ 8.76 (s, 1H), 8.50 (d, *J*=4 Hz, 1H), 8,00 (d, *J*=8 Hz, 1H), 7.72 (s, 1H), 7.63-7.37 (m, 9H), 6.98 (m, 2H), 5.95 (s, 2H), 3.77 (s, 3H).

Example 24

3-(4-Fluoro-3-methylphenyl)-5-(4-methoxyphenyl)-1-[3-(trifluoromethyl)-benzyl]indole-2-carboxylic acid

The title compound was prepared in accordance with Example 19 using 4-fluoro-3-methylphenylboronic acid and 5 mol% $Pd(PPh_3)_2Cl_2$.

^1H NMR (200 MHz, DMSO-d_6): δ 7.69-7.50 (m, 8H), 7.42 (m, 1H), 7.37-7.28 (m, 2H), 7.24-7.17 (m, 1H), 6.98 (m, 2H), 5.94 (s, 2H), 3.76 (s, 3H), 2.29 (d, *J*=2 Hz, 3H).

Example 25

3-(3,5-Dichlorophenyl)-5-(4-methoxyphenyl)-1-[3-(trifluoromethyl)-benzyl]indole-2-carboxylic acid

The title compound was prepared in accordance with Example 19 using 3,5-dichlorophenylboronic acid and 3.5 mol% $Pd(PPh_3)_2Cl_2$.

^1H NMR (200 MHz, $CDCl_3$): δ 7.63-7.58 (m, 2H), 7.53-7.44 (m, 4H), 7.40-7.34 (m, 5H), 7.14 (d, *J*=8 Hz, 1H), 6.97 (m, 2H), 5.82 (s, 2H), 3.84 (s, 3H).

Example 26

5-(2-Methoxyphenyl)-3-(3-nitrophenyl)-1-[3-(trifluoromethyl)benzyl]-indole-2-carboxylic acid

(a) 5-(2-Methoxyphenyl)indole-2-carboxylic acid ethyl ester

A mixture of 5-bromoindole-2-carboxylic acid ethyl ester (268 mg, 1 mmol), 2-methoxyphenylboronic acid (304 mg, 2 mmol), $Pd(PPh_3)_2Cl_2$ (35 mg, 50 nmol), Na_2CO_3 (159 mg, 1.5 mmol),and DME/H_2O/EtOH 7:3:2 (3 mL) was heated at 160°C for 8 minutes using microwave irradiation. The mixture was poured into water and extracted with EOAc. The combined extracts were dried over Na_2SO_4 and concentrated. The residue was crystallised from EtOH/H_2O to yield the sub-title compound (37%).

(b) 5-(2-Methoxyphenyl)-3-(3-nitrophenyl)-1-[3-(trifluoromethyl)benzyl]-indole-2-carboxylic acid

The title compound was prepared in accordance with Example 19(b), 19(c) and 19(d) using 3-nitrophenylboronic acid and 2.5 mol% $Pd(PPh_3)_2Cl_2$.

^1H NMR (200 MHz, DMSO-d_6): δ 13.31 (br s, 1H), 8.32 (m, 1H), 8.23 (m, 1H), 7.98 (d, *J*=8 Hz, 1H), 7.80-7.49 (m, 7H), 7.32-7.26 (m, 3H), 7.07 (d, *J*=8 Hz, 1H), 6.98 (t, *J*=8 Hz, 1H), 6.01 (s, 2H), 3.72 (s, 3H).

Example 27

5-(2-Methoxyphenyl)-3-(4-methoxyphenyl)-1-[3-(trifluoromethyl)benzyl]-indole-2-carboxylic acid

The title compound was prepared in accordance with Example 26 using 4-methoxyphenylboronic acid and 2.5 mol% $Pd(PPh_3)_2Cl_2$.

^1H NMR (200 MHz, DMSO-d_6): δ 12.98 (br s, 1H), 7.66-7.60 (m, 3H), 7.55 (t, *J*=8 Hz, 1H), 7.50-7.38 (m, 4H), 7.34-7.24 (m, 3H), 7.06 (d, *J*=8 Hz, 1H), 7.04-6.95 (m, 3H), 5.95 (s, 2H), 3.81 (s, 3H), 3.71 (s, 3H).

Example 28

3-(3,5-Dichlorophenyl)-5-(2-methoxyphenyl)-1-[3-(trifluoromethyl)-benzyl]indole-2-carboxylic acid

The title compound was prepared in accordance with Example 26 using 3,5-dichlorophenylboronic acid and 2.5 mol% $Pd(PPh_3)_2Cl_2$.

^1H NMR (200 MHz, DMSO-d_6): δ 7.72 (s, 1H), 7.65-7.56 (m, 5H), 7.54-7.51 (m, 2H), 7.46 (m, 1H), 7.35-7.27 (m, 3H), 7.10 (m, 1H), 6.99 (m, 1H), 5.96 (s, 2H), 3.73 (s, 3H).

Example 29

5-(3-Acetylphenyl)-3-(4-methoxyphenyl)-1-[3-(trifluoromethyl)benzyl]-indole-2-carboxylic acid

(a) 5-(3-Acetylphenyl)indole-2-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 26(a) using 3-acetylphenylboronic acid and 2.5 mol% $Pd(PPh_3)_2Cl_2$ and heating at 160°C for 10 min.

(b) 5-(3-Acetylphenyl)-3-(4-methoxyphenyl)-1-[3-(trifluoromethyl)benzyl]-indole-2-carboxylic acid

The title compound was prepared in accordance with Example 26(b) using 4-methoxyphenylboronic acid and 2.5 mol% $Pd(PPh_3)_2Cl_2$.

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.06 (br s, 1H), 8.10 (s, 1H), 7.89 (m, 2H), 7.80-7.67 (m, 3H), 7.65-7.54 (m, 4H), 7.44 (m, 2H), 7.28 (d, *J*=8 Hz, 1H), 7.03 (m, 2H), 5.98 (s, 2H), 3.82 (s, 3H), 2.63 (s, 3H).

Example 30

3,5-Bis(3-acetylphenyl)-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid

The title compound was prepared in accordance with Example 29 using 3-acetylphenylboronic acid and 2.5 mol% $Pd(PPh_3)_2Cl_2$

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.21 (br s, 1H), 8.10 (m, 2H), 7.98 (m, 1H), 7.89 (m, 2H), 7.84-7.78 (m, 2H), 7.74 (m, 1H), 7.70 (m, 1H), 7.67-7.52 (m, 5H), 7.30 (d, *J*=8 Hz, 1H), 6.02 (s, 2H), 2.64 (s, 3H), 2.62 (s, 3H).

Example 31

5-(3-Acetylphenyl)-3-phenyl-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid

The title compound was prepared in accordance with Example 29 using phenylboronic acid and 2.5 mol% $Pd(PPh_3)_2Cl_2$.

^1H NMR (200 MHz, DMSO-d_6): δ 13.14 (br s, 1H), 8.10 (m, 1H), 7.89 (m, 2H), 7.82-7.67 (m, 3H), 7.65-7.44 (m, 8H), 7.38 (m, 1H), 7.30 (d, *J*=Hz, 1H), 5.99 (s, 2H), 2.62 (s, 3H).

Example 32

5-(3-Acetylphenyl)-3-(4-pyridyl)-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid

The title compound was prepared in accordance with Example 29 using 4-pyridylboronic acid and 2.5 mol% $Pd(PPh_3)_2Cl_2$.

^1H NMR (200 MHz, DMSO-d_6): δ 8.65 (m, 2H), 8.13 (m, 1H), 7.91 (m, 2H), 7.85-7.80 (m, 1H), 7.77-7.73 (m, 2H), 7.66-7.51 (m, 6H), 7.30 (d, *J*=8 Hz, 1H), 6.01 (s, 2H), 2.63 (s, 3H).

Example 33

5-(3-Acetylphenyl)-3-(4-chlorophenyl)-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid

The title compound was prepared in accordance with Example 29 using chlorophenylboronic acid and 2.5 mol% $Pd(PPh_3)_2Cl_2$.

^1H NMR (200 MHz, DMSO-d_6): δ 13.22 (br s, 1H), 8.12 (m, 1H), 7.90 (m, 2H), 7.83-7.67 (m, 3H), 7.65-7.50 (m, 8H), 7.29 (d, *J*=8 Hz, 1H), 6.00 (s, 2H), 2.63 (s, 3H).

Example 34

5-(4-Chlorophenyl)-3-(3-pyridyl)-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid

(a) 5-(4-Chlorophenyl)indole-2-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 26(a) using 4-chlorophenylboronic acid and 4.0 mol% $Pd(PPh_3)_2Cl_2$ and heating at 160°C for 10 min.

(b) 1-(3-(Trifluoromethyl)benzyl)-5-(4-chlorophenyl)-3-(3-pyridyl)-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid

The title compound was prepared in accordance with Example 26(b) using 3-pyridylboronic acid and 2.5 mol% $Pd(PPh_3)_2Cl_2$.

Example 35

5-(4-Chlorophenyl)-3-(4-(hydroxymethyl)phenyl)-1-[3-(trifluoromethyl)-benzyl]indole-2-carboxylic acid

The title compound was prepared in accordance with Example 34 using 4-(hydroxymethyl)phenylboronic acid and 5 mol% $Pd(PPh_3)_2Cl_2$.

^1H NMR (200 MHz, DMSO-d_6): δ 7.74 (m, 2H), 7.66-7.58 (m, 4H), 7.55-7.26 (m, 9H), 5.95 (s, 2H), 5.29 (br s, 1H), 4.57 (s, 2H).

Example 36

5-(4-Chlorophenyl)-3-(4-fluoro-3-methylphenyl)-1-[3-(trifluoromethyl)-benzyl]indole-2-carboxylic acid

The title compound was prepared in accordance with Example 34 using 4-fluoro-3-methylphenylboronic acid and 5 mol% $Pd(PPh_3)_2Cl_2$.

Example 37

5-(4-Chlorophenyl)-3-(4-ethylphenyl)-1-[3-(trifluoromethyl)benzyl]indole-2-carboxylic acid

The title compound was prepared in accordance with Example 34 using 4-ethylphenylboronic acid and 5 mol% $Pd(PPh_3)_2Cl_2$.

^1H NMR (200 MHz, DMSO-d_6): δ 7.76-7.70 (m, 1H), 7.66-7.58 (m, 5H), 7.57-7.50 (m, 2H), 7.48-7.40 (m, 4H), 7.33-7.30 (m, 3H), 5.94 (s, 2H), 2.68 (q, *J*=8 Hz, 2H), 1.25 (t, *J*=8 Hz, 3H).

Example 38

6-(3-Aminophenyl)-3-phenyl-1-[(3-(trifluoromethoxy)benzyl]indole-2-carboxylic acid hydrochloride

(a) 6-(3-Aminophenyl)-3-phenyl-1-[(3-(trifluoromethoxy)benzyl]indole-2-carboxylic acid ethyl ester hydrochloride

6-(3-Nitrophenyl)-3-phenyl-1-[(3-(trifluoromethoxy)benzyl]-indole-2-carboxylic acid ethyl ester, prepared in accordance with the procedure in Example 1(a)-(d) from 6-bromoindole-2-carboxylic acid ethyl ester, 3-nitrophenylboronic acid and 3-(trifluoromethoxy)benzyl chloride (1.55 g, 2.76 mmol), in EtOAc (35 mL) was hydrogenated at ambient temperature and pressure over Pd-C (10%, 440 mg) until all starting material was consumed as judged by TLC. The mixture was filtered through Celite® and the filtrate concentrated. The residue was purified by chromatography, dissolved in anhydrous Et_2O, whereafter the sub-title compound was precipitated by the addition of an excess of HCl (4M) in dioxane. Yield: 955 mg (73%).

(b) 6-(3-Aminophenyl)-3-phenyl-1-[(3-(trifluoromethoxy)benzyl]indole-2-carboxylic acid hydrochloride

The title compound was prepared by hydrolysis of 6-(3-aminophenyl)-3-phenyl-1-[(3-(trifluoromethoxy)benzyl]-indole-2-carboxylic acid ethyl ester

in accordance with the procedure described in Example 2(b) (2M KOH (aq.), dioxane, 100°C, 1 h), followed by precipitation from an ethereal solution by addition of HCl (4M) in dioxane as described above.

^{1}H NMR (200 MHz, DMSO-d_6): δ 11.5-9.6 (3H, br s), 7.94 (1H, s), 7.67-7.05 (15H, m), 5.99 (2H, s), 4.5-3.0 (1H, br s).

Example 39

6-[3-(2,2-Dimethylpropionylamino)phenyl]-3-phenyl-1-[3-(trifluoromethoxy)benzyl]indole-2-carboxylic acid

(a) 6-[3-(2,2-Dimethylpropionylamino)phenyl]-3-phenyl-1-[3-(trifluoromethoxy)benzyl]indole-2-carboxylic acid ethyl ester

Pivaloyl chloride (156 μL, 1.27 mmol) was added over 5 min to a stirred solution of 6-(3-aminophenyl)-3-phenyl-1-[3-(trifluoromethoxy)benzyl]-indole-2-carboxylic acid ethyl ester hydrochloride (600 mg, 1.06 mmol; see Example 38(a)), DMAP (65 mg, 0.53 mmol), Et_3N (530 μL, 3.8 mmol), and dry CH_2Cl_2 (10 mL). The mixture was stirred at room temperature overnight whereafter another portion of pivaloyl chloride (0.156 μL, 1.27 mmol) and Et_3N (530, μL, 3.8 mmol) was added. After 2 h at room temperature, the mixture was diluted with CH_2Cl_2 and washed with HCl (aq., 1M), $NaHCO_3$ (aq., sat.) and brine, and concentrated. The residue was treated with pentane to give the title compound as a white solid (480 mg, 74%).

(b) 6-[3-(2,2-Dimethylpropionylamino)phenyl]-3-phenyl-1-[3-(trifluoromethoxy)benzyl]indole-2-carboxylic acid

The title compound was prepared by hydrolysis of 6-[3-(2,2-dimethylpropionylamino)phenyl]-3-phenyl-1-[3-(trifluoromethoxy)benzyl]indole-2-carboxylic acid ethyl ester in accordance with the procedure described in Example 1(e) (2M KOH (aq.), dioxane, 120 °C, 2 h).

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.0 (1H, s), 9.29 (1H, s), 7.98-7.96 (1H, m), 7.90 (1H, s), 7.72-7.66 (1H, m), 7.59-7.36 (10H, m), 7.26-7.19 (2H, m), 7.11-7.07 (1H, m), 6.00 (2H, s), 1.24 (9H, s).

Example 40

6-(3-(Methanesulfonylamino)phenyl)-3-phenyl-1-[3-(trifluoromethoxy)-benzyl]indole-2-carboxylic acid

The title compound was prepared in accordance with the procedure in Example 39 using methanesulfonyl chloride instead of pivaloyl chloride.

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.2-12.9 (1H, br s), 9.80 (1H, s), 7.88-7.86 (1H, m), 7.56-7.35 (11H, m), 7.24-7.15 (3H, m), 7.10-7.05 (1H, m), 5.97 (2H, s), 3.00 (3H, s).

Example 41

6-(3-But-3-enylaminophenyl)-3-phenyl-1-[(3-(trifluoromethoxy)benzyl]-indole-2-carboxylic acid

(a) 6-(3-But-3-enylaminophenyl)-3-phenyl-1-[(3-(trifluoromethoxy)benzyl]indole-2-carboxylic acid ethyl ester

4-Bromo-1-butene (143 mg, 1.06 mmol) was added to a mixture of 6-(3-aminophenyl)-3-phenyl-1-[3-(trifluoromethoxy)benzyl]indole-2-carboxylic acid ethyl ester hydrochloride (400 mg, 0.71 mmol; see Example 38(a)), NaI (317 mg, 2.12 mmol), K_2CO_3 (390 mg, 2.84 mmol), and dry DMF (3 mL). The mixture was heated at 100°C for 12 h, allowed to cool and poured into water. The mixture was extracted with EtOAc and the combined extracts were washed with water, brine, dried over Na_2CO_3 and concentrated. The residue was purified by chromatography to give the title compound (173 mg, 42%).

(b) 6-(3-But-3-enylaminophenyl)-3-phenyl-1-[(3-(trifluoromethoxy)benzyl]indole-2-carboxylic acid

The title compound was prepared by hydrolysis of 6-(3-but-3-enylaminophenyl)-3-phenyl-1-[(3-(trifluoromethoxy)benzyl]indole-2-carboxylic acid ethyl ester in accordance with the procedure described in Example 1(e) (NaOH (aq., 40%), DMF, room temperature, 2 h).

^{1}H NMR (200 MHz, DMSO-d_6): δ 7.79 (1H, s), 7.51-7.31 (8H, m), 7.24-7.06 (4H, m), 6.84-6.80 (2H, m), 6.57-6.52 (1H, m), 5.97 (2H, s), 5.88 (1H, ddt, *J*=17.2, 10.3, 6.7 Hz), 5.15-4.98 (2H, m), 3.11 (2H, t, *J*=7.2 Hz) 2.30 (2H, q, *J*=6.9 Hz).

Example 42

6-[3-(Allylmethanesulfonylamino)phenyl]-3-phenyl-1-(3-trifluoromethoxy-benzyl)indole-2-carboxylic acid

Allyl iodide (54 μL, 0.59 mmol) was added to a mixture of 6-[3-(methanesulfonylamino)phenyl]-3-phenyl-1-(3-trifluoromethoxy-benzyl)indole-2-carboxylic acid ethyl ester (178 mg, 0.29 mmol; see Example 40), Cs_2CO_3 (333 mg, 1.02 mmol), and dry DMF (2.5 mL). The mixture was heated at 85°C for 30 min using microwave irradiation, allowed to cool and poured into water. The mixture was extracted with EtOAc and the combined extracts were washed with brine, dried over Na_2CO_3 and concentrated. The residue was hydrolyzed in accordance with the procedure described in Example 2(b) (2M KOH (aq.), dioxane, 110 °C, 55 min) to give the title compound (140 mg, 78%).

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.08 (1H, s), 7.94 (1H, s), 7.68-7.63 (2H, m), 7.58-7.34 (10H, m), 7.25-7.20 (2H, m), 7.12-7.07 (1H, m), 6.01 (2H, s), 5.79 (1H, ddt, *J*=17.1, 10.2, 5.9 Hz), 5.19 (1H, dd, *J*=17.1, 1.5 Hz), 5.07 (1H, dd, *J*=10.2, 1.5 Hz), 4.35 (2H, d, J=5.9 Hz), 3.05 (3H, s).

Example 43

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-[3-(4-methoxyphenyl)-propionylamino]indole-2-carboxylic acid

(a) 3-Amino-1-(3-chlorobenzyl)-6-(3,5-difluorophenyl)indole-2-carboxylic acid ethyl ester

A mixture of 3-amino-6-bromo-1-(3-chlorobenzyl)indole-2-carboxylic acid ethyl ester (1.04 g, 2.25 mmol, see Example 54(b)) $Pd(OAc)_2$ (31 mg, 0.14 mmol), tri-*o*-tolylphosphine (84 mg, 0.28 mmol), K_2CO_3 (1.33 g, 9.64 mmol) and toluene (30 mL) was stirred under argon at room temperature for 10 min whereafter 3,5-dimethoxyphenylboronic acid (0.78 g, 4.13 mmol) and EtOH (10 mL) was added. The mixture was heated at reflux for 2.5 h allowed to cool and filtered through Celite®. The filter cake was washed with EtOAc and the combined filtrates were washed with $NaHCO_3$ (aq., sat.). The aqueous phase was extracted with EtOAc and the combined organic phases were washed with water, brine and dried over Na_2CO_3. Concentration and purification by chromatography gave the title compound (1.28 g, 98%).

(b) 1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-[3-(4-methoxyphenyl)-propionylamino]indole-2-carboxylic acid ethyl ester

DMAP (22.3 mg, 0.18 mmol) and Et_3N (154 µL, 1.1 mmol) were added at room temperature to a stirred mixture of 3-amino-1-(3-chlorobenzyl)-6-(3,5-difluorophenyl)indole-2-carboxylic acid ethyl ester (150 mg, 0.37 mmol), 3-(4-methoxyphenyl)propionyl chloride (109 mg, 0.55 mmol) and MeCN (3.5 mL). The mixture was stirred at room temperature overnight, poured into HCl (aq., 1M) and extracted with EtOAc. The combined extracts were washed with $NaHCO_3$ (aq., sat.), dried over Na_2CO_3 and concentrated. The sub-title compound was obtained by crystallisation of the residue from EtOAc/benzene (108 mg, 50 %).

(c) 1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-[3-(4-methoxyphenyl)-propionylamino]indole-2-carboxylic acid

The title compound was prepared by hydrolysis of 1-(3-chlorobenzyl)-6-(3,5-difluorophenyl)-3-[3-(4-methoxyphenyl)-propionylamino]indole-2-carboxylic acid ethyl ester (108 mg, 0.18 mmol) according to the procedure described in Example 2(b) (KOH (aq., 2M), dioxane, 60 °C 50 min then 100 °C 30 min). Yield 75 mg (73 %).

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.6-13.2 (1H, br s), 9.73 (1H, s), 8.09-8.03 (1H, m), 7.57-6.86 (13H, m), 5.94 (2H, s), 3.73 (3H, s), 2.95-2.86 (2H, m), 2.73-2.64 (2H, m).

The following Examples 44 to 53 were made in accordance with the procedure in Example 43 using the appropriate acid chloride or sulfonyl chloride.

Example 44

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-[(3,5-dimethyladamantane-1-carbonyl)amino]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.8-13.2 (1H, br s), 9.52 (1H, s), 8.04 (1H, s), 7.81 (1H, d, *J*=8.6 Hz), 7.60-7.48 (3H, m), 7.34-7.16 (3H, m), 7.11-7.10 (1H, m), 6.98-6.90 (1H, m), 5.94 (2H, s), 2.16-2.11 (1H, m), 1.81-1.80 (2H, m), 1.68-1.53 (4H, m), 1.45-1.30 (4H, m), 1.23-1.14 (2H, m), 0.87 (6H, s).

Example 45

3-(2-Adamant-1-ylacetylamino)-1-(3-chlorobenzyl)-6-(3,5-difluorophenyl)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.2 (1H, br s), 9.56 (1H, s), 8.04 (1H, s), 7.70 (1H, d, *J*=8.6 Hz), 7.59-7.49 (3H, m), 7.33-7.07 (4H, m), 6.94-

6.89 (1H, m), 5.90 (2H, s), 2.14 (2H, s), 1.96-1.92 (3H, m), 1.69-1.63 (12H, m).

Example 46

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-(toluene-4-sulfonylamino)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.8-12.8 (1H, br s), 9.33 (1H, s), 8.02 (1H, s), 7.78 (1H, d, *J*=8.6 Hz), 7.58-7.52 (3H, m), 7.44-7.38 (2H, m), 7.34-7.17 (4H, m), 6.99 (2H, s), 6.79-6.73 (1H, m), 5.84 (2H, s), 2.33 (3H, s).

Example 47

1-(3-Chlorobenzyl)-3-(2-cyclohexylideneacetylamino)-6-(3,5-difluorophenyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.7-12.8 (1H, br s), 9.62 (1H, s), 8.03 (1H, s), 7.74 (1H, d, *J*=8.6 Hz), 7.58-7.48 (3H, m), 7.33-7.23 (2H, m), 7.18 (1H, ddd, *J*=9.3, 2.3, 2.3 Hz), 7.09-7.07 (1H, m), 6.97-6.89 (1H, m), 5.94 (1H, s), 5.91 (2H, s), 2.89-2.83 (2H, m), 2.21-2.16 (2H, m), 1.65-1.52 (6H, m).

Example 48

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-[2-(3,3,5,5-tetramethylcyclohexylidene)acetylamino]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.6-13.1 (1H, br s), 9.67 (1H, s), 8.06 (1H, s), 7.74 (1H, d, *J*=8.6 Hz), 7.61-7.51 (3H, m), 7.35-7.16 (3H, m), 7.11-7.09 (1H, m), 6.99-6.91 (1H, m), 6.07 (1H, s), 5.94 (2H, s), 2.70 (2H, s), 1.99 (2H, s), 1.33 (2H, s), 0.97-0.96 (12H, m).

Example 49

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-[2-(3,3,5,5-tetramethylcyclohexylidene)acetylamino]indole-2-carboxylic acid sodium salt

^{1}H NMR (200 MHz, DMSO-d_6): δ 12.13 (1H, s), 8.38 (1H, d, J= 8.6 Hz), 7.76 (1H, s), 7.48-7.42 (2H, m), 7.36-7.29 (1H, m), 7.25-7.15 (3H, m), 7.11-7.04 (2H, m), 6.17 (2H, s), 5.85 (1H, s), 2.74 (2H, s), 1.97 (2H, s), 1.31 (2H, s), 0.97-0.92 (12H, m).

Example 50

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-(4-isopropoxybenzoylamino)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.6-13.2 (1H, br s), 10.13 (1H, s), 8.08 (1H, s), 8.03-7.96 (2H, m), 7.83 (1H, d, *J*=8.6 Hz), 7.62-7.51 (3H, m), 7.35-7.12 (4H, m), 7.08-7.01 (2H, m), 6.99-6.93 (1H, m), 5.96 (2H, s), 4.74 (1H, septet, *J*=6.1 Hz), 1.29 (6H, d, *J*=6.1 Hz).

Example 51

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-(4-isopropoxybenzoylamino)-indole-2-carboxylic acid sodium salt

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.14 (1H, br s), 8.49 (1H, d, *J*=8.4 Hz), 7.98-7.91 (2H, m), 7.81 (1H, s), 7.51-7.44 (2H, m), 7.40-7.33 (1H, m), 7.25-7.17 (3H, m), 7.16-6.99 (4H, m), 6.19 (2H, s), 4.72 (1H, septet, *J*=6.0 Hz), 1.28 (6H, d, *J*=6.0 Hz).

Example 52

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-[4-(trifluoromethyl)benzoylamino]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.7-13.1 (1H, br s), 10.49 (1H, s), 8.23 (2H, m), 8.11 (1H, s), 7.93 (2H, m), 7.77 (1H, d, *J*=8.6 Hz), 7.59-7.53 (3H, m), 7.35-7.09 (4H, m), 6.99-6.94 (1H, m), 5.97 (2H, s).

Example 53

1-(3-Chlorobenzyl)-3-[(6-chloropyridine-3-carbonyl)amino]-6-(3,5-di-fluorophenyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 14.21-14.16 (1H, br s), 8.99 (1H, d, *J*=2.2 Hz), 8.56 (1H, d, *J*=8.6 Hz), 8.37 (1H, dd, *J*=8.4, 2.6 Hz), 7.83-7.82 (1H, m), 7.74 (1H, d, *J*=8.2 Hz), 7.51-7.36 (3H, m), 7.30-7.06 (5H, m), 6.21 (2H, s).

Example 54

3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-6-[4-(methylsulfonyl)-phenyl]indole-2-carboxylic acid

(a) 6-Bromo-1-(3-chlorobenzyl)-3-nitroindole-2-carboxylic acid ethyl ester

$Cu(NO_3)_2$ x2.5 H_2O (2.26 g, 9.74 mmol) was added to Ac_2O (10 mL) at 5 °C. The mixture was stirred until a homogenous solution was formed whereafter a solution 6-bromo-1-(3-chlorobenzyl)indole-2-carboxylic acid ethyl ester, prepared from 6-bromoindole-2-carboxylic acid ethyl ester and 3-chlorobenzyl chloride in accordance with the procedure in Example 1(c), (4.72 g, 12.02 mmol), in Ac_2O (20 mL) was added dropwise. The mixture was allowed to come to room temperature and was stirred for 1.5 h and filtered. The filtrate was poured onto ice and was left to stir overnight. The precipitate was collected and dried to give the sub-title compound (4.82 g, 92%).

(b) 3-Amino-6-bromo-1-(3-chlorobenzyl)indole-2-carboxylic acid ethyl ester

A mixture of 6-bromo-1-(3-chlorobenzyl)-3-nitroindole-2-carboxylic acid ethyl ester (4.82 g, 11.01 mmol), Fe-powder (3.15 g, 56.3 mmol), NH_4Cl (aq., sat., 75 mL) and isopropanol (160 mL) was heated at reflux for 2 h,

whereafter additional portions of Fe-powder (3.15 g, 56.3 mmol) and NH_4Cl (aq., sat., 75 mL) were added. The mixture was heated for an additional 2 h, allowed to cool and filtered through Celite®. The filter cake was washed with EtOAc and the combined filtrates were extracted with EtOAc. The combined extracts were washed with water, brine and dried over Na_2CO_3. Concentration and purification by chromatography gave the title compound (3.99 g, 89%).

(c) 6-Bromo-3-(4-chlorobenzoylamino)-1-(3-chlorobenzyl)indole-2-carboxylic acid ethyl ester

A mixture of 3-amino-6-bromo-1-(3-chlorobenzyl)indole-2-carboxylic acid ethyl ester (2.00 g, 4.91 mmol), 4-chlorobenzoyl chloride (1.72 g, 9.82 mmol), DMAP (300 mg, 2.46 mmol), Et_3N (1.38 mL, 9.82 mmol) and MeCN (50 mL) was stirred at room temperature for 24 h. The mixture was poured into water and extracted with EtOAc. The combined extracts were washed with water, brine and dried over Na_2CO_3. Concentration, crystallisation from EtOH/EtOAc (1:1) and chromatography gave the title compound.

(d) 3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-6-[4-(methylsulfonyl)-phenyl]indole-2-carboxylic acid ethyl ester

A mixture of 6-bromo-3-(4-chlorobenzoylamino)-1-(3-chlorobenzyl)indole-2-carboxylic acid ethyl ester (160 mg, 0.29 mmol), 4-(methanesulfonyl)-phenylboronic acid (87.9 mg, 0.44 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), tri-*o*-tolylphosphine (8.8 mg, 0.029 mmol), K_3PO_4 (215 mg, 1.02 mmol), toluene (3 mL) and EtOH (0.5 mL) was stirred at room temperature for 20 min and heated at 90 °C for 3h. The mixture was allowed to cool, poured into $NaHCO_3$ (aq., sat.) and extracted with EtOAc. The combined extracts were washed brine and dried over Na_2CO_3. Concentration and purification by chromatography gave the title compound (120 mg, 67%).

(e) 3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-6-[4-(methylsulfonyl)-phenyl]indole-2-carboxylic acid

The title compound was prepared by hydrolysis of 3-(4-chlorobenzoylamino)-1-(3-chlorobenzyl)-6-[4-(methylsulfonyl)phenyl]indole-2-carboxylic acid ethyl ester (120 mg, 0.19 mmol) according to the procedure described in Example 1(e). Yield 84 mg (74%).

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.6-13.4 (1H, br s), 10.36 (1H, s), 8.12-7.97 (7H, m), 7.83 (1H, d, *J*=8.4 Hz), 7.69-7.61 (2H, m), 7.57 (1H, d, *J*=8.7 Hz), 7.38-7.25 (2H, m), 7.17-7.13 (1H, m), 7.03-6.96 (1H, m), 6.00 (2H, s), 3.26 (3H, s).

The following Examples 55 to 64 were made in accordance with the procedure in Example 54 using the appropriately substituted phenylboronic acids.

Example 55

3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-6-[4-(methylthio)phenyl]-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.7-13.1 (1H, br s), 10.35 (1H, s), 8.12-8.04 (2H, m), 7.93 (1H, s), 7.77 (1H, d, *J*=8.5 Hz), 7.74-7.61 (4H, m), 7.47 (1H, d, *J*=8.5 Hz), 7.39-7.25 (4H, m), 7.16-7.12 (1H, m), 7.04-6.97 (1H, m), 5.97 (2H, s), 2.51 (3H, s).

Example 56

3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-6-(4-vinylphenyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.6-13.2 (1H, br s), 10.35 (1H, s), 8.12-8.04 (2H, m), 7.97 (1H, s), 7.78 (1H, d, *J*=8.4 Hz), 7.78-7.72 (2H, m), 7.69-7.62 (2H, m), 7.61-7.54 (2H, m), 7.51 (1H, d, *J*=8.6 Hz), 7.38-7.25 (2H, m),

7.18-7.13 (1H, m), 7.05-6.98 (1H, m), 6.79 (H, dd, *J*=17.8, 11.0 Hz), 5.98 (2H, s), 5.90 (1H, d, *J*=17.8 Hz), 5.29 (1H, d, 11.0 Hz).

Example 57

3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-6-(4-isopropoxyphenyl)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.3 (1H, br s), 10.35 (1H, s), 8.12-8.03 (2H, m), 7.85 (1H, s), 7.75 (1H, d, *J*=8.5 Hz), 7.70-7.61 (4H, m), 7.43 (1H, d, *J*=8.7 Hz), 7.38-7.25 (2H, m), 7.15-7.11 (1H, m), 7.05-6.96 (3H, m), 5.96 (2H, s), 4.67 (1H, septet, *J*=6.0 Hz), 1.28 (6H, d, *J*=6.0 Hz).

Example 58

6-(4-*tert*-Butylphenyl)-3-(4-chlorobenzoylamino)-1-(3-chlorobenzyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.3 (1H, br s), 10.34 (1H, s), 8.12-8.03 (2H, m), 7.88 (1H, s), 7.76 (1H, d, *J*=8.4 Hz), 7.70-7.60 (4H, m), 7.52-7.42 (3H, m), 7.38-7.25 (2H, m), 7.17-7.13 (1H, m), 7.05-6.98 (1H, m), 5.96 (2H, s), 1.31 (9H, s).

Example 59

3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-6-[4-(trifluoromethyl)-phenyl]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.6-13.3 (1H, br s), 10.43 (1H, s), 8.12-8.04 (3H, m), 8.03-7.95 (2H, m), 7.87-7.78 (3H, m), 7.69-7.61 (2H, m), 7.54 (1H, dd, *J*=8.5, 1.0 Hz), 7.38-7.25 (2H, m), 7.16-7.12 (1H, m), 7.03-6.96 (1H, m), 6.00 (2H, s).

Example 60

3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-6-[4-(trifluoromethoxy)-phenyl]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.6-13.2 (1H, br s), 10.39 (1H, s), 8.10-8.02 (2H, m), 7.97 (1H, s), 7.89-7.82 (2H, m), 7.79 (1H, d, *J*=8.5 Hz), 7.67-7.59 (2H, m), 7.50-7.41 (3H, m), 7.36-7.23 (2H, m), 7.14-7.10 (1H, m), 7.02-6.95 (1H, m), 5.96 (2H, s).

Example 61

3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-6-(4-cyclohexylphenyl)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, acetone-d_6): δ 11.9-11.5 (1H, br s), 8.61-8.52 (1H, m), 8.24-8.15 (2H, m), 7.71 (1H, s), 7.66-7.58 (2H, m), 7.58-7.49 (2H, m), 7.45-7.37 (1H, m), 7.34-7.12 (6H, m), 6.16 (2H, s), 2.64-2.47 (1H, m), 1.93-1.68 (5H, m), 1.60-1.22 (5H, m).

Example 62

6-(4-Butylphenyl)-3-(4-chlorobenzoylamino)-1-(3-chlorobenzyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.2 (1H, br s), 8.49 (1H, d, *J*=8.6 Hz), 8.12-8.00 (2H, m), 7.70-7.59 (4H, m), 7.57 (1H, s), 7.37-7.17 (6H, m), 7.16-7.08 (1H, m), 6.20 (2H, s), 2.61 (2H, t, *J*=7.4 Hz), 1.67-1.49 (2H, m), 1.42-1.22 (2H, m), 0.91 (3H, t, *J*=7.2 Hz).

Example 63

3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-6-(4-cyanophenyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.3-13.1 (1H, br s), 8.52 (1H, d, *J*=8.6 Hz), 8.10-8.01 (2H, m), 7.98-7.84 (5H, m), 7.68-7.60 (2H, m), 7.43 (1H, dd, *J*=8.6, 0.9 Hz), 7.34-7.18 (3H, m), 7.14-7.07 (1H, m), 6.21 (2H, s).

Example 64

3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-6-(4-chlorophenyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.8-13.2 (1H, br s), 11.8-11.4 (1H, br s), 8.14-8.02 (3H, m), 7.87 (1H, s), 7.81-7.73 (2H, m), 7.68-7.60 (2H, m), 7.56-7.48 (2H, m), 7.42 (1H, dd, *J*=8.7, 1.1 Hz), 7.36-7.22 (2H, m), 7.19-7.14 (1H, m), 7.08-7.00 (1H, m), 6.07 (2H, s).

The following Examples 65 to 109 were prepared by analogous techniques to those described herein.

Example 65

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-(4-methoxybenzoylamino)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 10.19 (1H, s), 8.14-8.02 (3H, m), 7.86 (1H, d, *J*=8.6 Hz), 7.64-7.53 (3H, m), 7.39-7.07 (6H, m), 7.03-6.96 (1H, m), 6.00 (2H, s), 3.87 (3H, s).

Example 66

1-(3-Chlorobenzyl)-3-(4-methoxybenzoylamino)-6-naphth-1-ylindole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 10.21 (1H, s), 8.09-7.91 (4H, m), 7.86 (1H, d, *J*=8.4 Hz), 7.66-7.69 (2H, m), 7.62-7.51 (2H, m), 7.48 (1H, d, *J*=1.2 Hz), 7.46-7.29 (3H, m), 7.23 (1H, dd, *J*=8.4, 1.2 Hz), 7.17-7.14 (1H, m), 7.13-7.05 (2H, m), 7.04-6.97 (1H, m) 5.91 (2H, s), 3.84 (3H, s).

Example 67

6-Benzo[1,3]dioxol-5-yl-1-(3-cyanobenzyl)-3-(3-phenylpropionylamino)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 9.7 (1H, s), 7.79 (1H, s), 7.70-7.64 (1H, m), 7.56-7.14 (12H, m), 6.97 (1H, d, *J*=8.1 Hz), 6.03 (2H, s), 5.92 (2H, s), 3.00-2.90 (2H, m), 2.75-2.64 (2H, m).

Example 68

1-(3-Chlorobenzyl)-6-naphth-1-yl-3-pentanoylaminoindole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.37 (1H, s), 9.67 (1H, s), 8.02-7.91 (2H, m), 7.74-7.65 (3H, m), 7.61-7.25 (6H, m), 7.22 (1H, dd, *J*=8.4, 0.9 Hz), 7.12-7.09 (1H, m), 7.02-6.93 (1H, m), 5.86 (2H, s), 2.41 (2H, t, *J*=7.2 Hz), 1.72-1.56 (2H, m), 1.49-1.29 (2H, m) , 0.93 (3H, t, *J*=7.3 Hz).

Example 69

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-pentanoylaminoindole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.4 (1H, br s), 9.67 (1H, s), 8.08 (1H, s), 7.71 (1H, d, *J*=8.5 Hz), 7.62-7.51 (3H, m), 7.37-7.18 (3H, m), 7.13-7.09 (1H, m), 7.00-6.92 (1H, m), 5.95 (2H, s), 2.42 (2H, t, *J*=7.3 Hz), 1.73-1.58 (2H, m), 1.49-1.31 (2H, m), 0.95 (3H, t, *J*=7.3 Hz).

Example 70

3-[(Biphenyl-4-carbonyl)amino]-1-(3-chlorobenzyl)-6-(3,5-difluorophenyl)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.6-12.4 (1H, br s), 10.70 (1H, s), 8.21-8.06 (3H, m), 7.96 (1H, d, *J*=8.6 Hz), 7.92-7.85 (2H, m), 7.84-7.77 (2H, m), 7.63-7.17 (10H, m), 7.06-6.99 (1H, m), 6.04 (2H, s).

Example 71

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-[2-(4-methoxyphenyl)acetyl-amino]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 9.81 (1H, s), 8.03 (1H, s), 7.63 (1H, d, *J*=8.6 Hz), 7.59-7.45 (3H, m), 7.35-7.13 (5H, m), 7.09-7.05 (1H, m), 6.95-6.84 (3H, m), 5.91 (2H, s), 3.73 (3H, s), 3.66 (2H, s).

Example 72

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-phenylindole-2-carboxylic acid.

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.10 (1H, s), 8.11 (1H, s), 7.60-7.43 (8H, m), 7.42-7.14 (5H, m), 7.03-6.95 (1H, m), 5.96 (2H, s).

Example 73

6-Benzo[1.3]dioxol-5-yl-1-(3-cyanobenzyl)-3-[4-(dimethylamino)butyryl-amino]indole-2-carboxylic acid hydrochloride

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.8-12.8 (1H, br s), 9.89 (1H, s), 7.87-7.84 (1H, m), 7.75-7.67 (2H, m), 7.54 (1H, d, *J*=8.1 Hz), 7.51-7.39 (2H, m), 7.36 (1H, d, *J*=1.7 Hz), 7.34-7.28 (1H, m), 7.23 (1H, dd, *J*=8.2, 1.7 Hz), 7.02 (1H, d, *J*=8.1 Hz), 6.08 (2H, s), 5.97 (2H, s), 3.19-3.08 (2H, m), 2.79 (6H, s), 2.58-2.48 (2H, m, overlapped with DMSO signal), 2.11-1.94 (2H, m).

Example 74

6-Benzo[1.3]dioxol-5-yl-3-(3-phenylacryloylamino)-1-[3-(2*H*-tetrazol-5-yl)benzyl]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 9.95 (1H, s), 7.89-7.82 (3H, m), 7.71 (1H, d, *J*=8.6 Hz), 7.68-7.35 (8H, m), 7.33 (1H, d, *J*=1.7 Hz), 7.23-7.14 (2H, m), 7.06 (1H, d, *J*=15.7 Hz), 6.97 (1H, d, *J*=8.2 Hz), 6.03 (2H, s), 6.01 (2H, s).

Example 75

1-(3-Chlorobenzyl)-5-(4-cyanophenyl)-3-(3,5-dimethoxybenzoylamino)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.8-13.1 (1H, br s), 10.23 (1H, s), 8.08 (1H, s), 7.88 (4H, s), 7.75 (2H, s), 7.38-7.26 (2H, m), 7.24-7.17 (2H, m), 7.16-7.11 (1H, m), 7.05-6.95 (1H, m), 6.76-6.69 (1H, m), 5.90 (2H, s), 3.81 (6H, s).

Example 76

1-(3-Chlorobenzyl)-3-pentanoylamino-6-[4-(trifluoromethyl)phenyl]-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 9.83 (1H, s), 7.96-7.73 (6H, m), 7.47 (1H, d, J= 8.7 Hz), 7.33-7.21 (2H, m), 7.10-7.07 (1H, m), 6.97-6.92 (1H, m), 5.93 (2H, s), 2.38 (2H, t, J=7.2 Hz), 1.69-1.55 (2H, m), 1.46-1.28 (2H, m), 0.91 (3H, t, J=7.3 Hz).

Example 77

1-(3-Chlorobenzyl)-3-[(3,3,5,5-tetramethylcyclohexanecarbonyl)amino]-6-[4-(trifluoromethyl)phenyl]-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.2 (1H, br s), 9.68 (1H, s), 8.03-8.00 (1H, m), 7.99-7.94 (2H, m), 7.84-7.80 (2H, m), 7.70 (1H, d, J=8.5 Hz), 7.51 (1H, d, J=8.5 Hz), 7.35-7.25 (2H, m), 7.09 (1H, s), 7.01-6.94 (1H, m), 5.93 (2H, s), 2.85 (1H, t, J=12.4 Hz) 1.63 (2H, d, J=12.4 Hz), 1.34-1.21 (3H, m), 1.12-1.09 (1H, m), 1.06 (6H, s), 0.94 (6H, s).

Example 78

3-Benzoylamino-1-(3-chlorobenzyl)-5-(4-cyanophenyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 10.33 (1H, s), 8.13-8.01 (3H, m), 7.88 (4H, s), 7.77-7.73 (2H, m), 7.64-7.49 (3H, m), 7.38-7.26 (2H, m), 7.17-7.12 (1H, m), 7.04-6.96 (1H, m), 5.90 (2H, s).

Example 79

5-(3-Chlorophenyl)-3-phenyl-1-[(3-(trifluoromethoxy)benzyl]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.2-13.0 (1H, br s), 7.78-7.70 (1H, m), 7.69-7.62 (3H, m), 7.60-7.30 (9H, m), 7.28-7.14 (2H, m), 7.10-7.02 (1H, m), 5.92 (2H, s).

Example 80

5-(2-Chlorophenyl)-3-phenyl-1-[(3-(trifluoromethoxy)benzyl]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.2-13.0 (1H, br s), 7.75-7.67 (1H, m), 7.56-7.19 (14H, m), 7.15-7.07 (1H, m), 5.93 (2H, s).

Example 81

5-(4-Chlorophenyl)-3-phenyl-1-[(3-(trifluoromethoxy)benzyl]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.2-13.0 (1H, br s), 7.77-7.56 (5H, m), 7.54-7.30 (8H, m), 7.27-7.13 (2H, m), 7.10-7.02 (1H, m), 5.92 (2H, s).

Example 82

5-(2-Chlorophenyl)-3-pentanoylamino-1-[(3-(trifluoromethoxy)benzyl]-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.2 (1H, br s), 9.63 (1H, s), 7.69-7.58 (2H, m), 7.58-7.50 (1H, m), 7.48-7.31 (5H, m), 7.27-7.17 (1H, m), 7.13 (1H, s), 7.03 (1H, d, *J*=7.7 Hz), 5.87 (2H, s), 2.36 (2H, t, *J*=7.3 Hz), 1.67-1.47 (2H, m), 1.44-1.23 (2H, m), 0.88 (3H, t, *J*=7.2 Hz).

Example 83

5-(3-Chlorophenyl)-3-pentanoylamino-1-[(3-(trifluoromethoxy)benzyl]-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.4-13.2 (1H, br s) 9.67 (1H, s) 7.86 (1H, s) 7.74-7.55 (4H, m) 7.53-7.33 (3H, m) 7.27-7.16 (1H, m) 7.09 (1H, s) 6.98 (1H, d, *J*=7.8 Hz) 5.87 (2H, s) 2.40 (2H, t, *J*=7.3 Hz) 1.72-1.50 (2H, m) 1.48-1.27 (2H, m) 0.91 (3H, t, *J*=7.2 Hz).

Example 84

5-(4-Chlorophenyl)-3-pentanoylamino-1-[(3-(trifluoromethoxy)benzyl]-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.4-13.1 (1H, br s), 9.65 (1H, s), 7.83 (1H, s), 7.72-7.56 (4H, m), 7.55-7.45 (2H, m), 7.40 (1H, dd, *J*=8.0 and 8.0 Hz), 7.25-7.16 (1H, m), 7.09 (1H, s), 6.97 (1H, d, *J*=8.0 Hz), 5.86 (2H, s), 2.40 (2H, t, *J*=7.2 Hz), 1.70-1.50 (2H, m), 1.48-1.28 (2H, m), 0.91 (3H, t, *J*=7.2 Hz).

Example 85

1-(3-Chlorobenzyl)-5-(4-chlorophenyl)-3-phenylindole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.2-13.0 (1H, br s), 7.77-7.57 (5H, m), 7.54-7.29 (9H, m), 7.22 (1H, s), 7.05-6.97 (1H, m), 5.87 (2H, s).

Example 86

5-(4-Chlorophenyl)-1-(3,5-dimethylbenzyl)-3-phenylindole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.1-13.0 (1H, br s), 7.73-7.57 (5H, m), 7.53-7.30 (7H, m), 6.85 (1H, s), 6.74 (2H, s), 5.77 (2H, s), 2.17 (6H, s).

Example 87

5-(4-Chlorophenyl)-1-(3,5-difluorobenzyl)-3-phenylindole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.2-13.0 (1H, br s), 7.76-7.58 (5H, m), 7.55-7.31 (17H, m), 7.12 (1H, t, *J*=9.4, 2.5 Hz), 6.86-6.73 (2H, m), 5.89 (2H, s).

Example 88

6-Benzo[1,3]dioxol-5-yl-3-pentanoylamino-1-(3-phenoxybenzyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.3 (1H, br s), 9.73 (1H, br s), 7.78 (1H, s), 7.66 (1H, d, *J*=8.4 Hz), 7.42-7.17 (6H, m), 7.16-7.07 (1H, m), 7.01 (1H, d, *J*=8.2 Hz), 6.99-6.91 (2H, m), 6.84-6.76 (3H, m), 6.09 (2H, s), 5.93 (2H, s), 2.41 (2H, t, *J*=7.0 Hz), 1.73-1.56 (2H, m), 1.50-1.30 (2H, m), 0.95 (3H, t, *J*=7.2 Hz).

Example 89

6-Benzo[1,3]dioxol-5-yl-1-(9*H*-fluoren-2-ylmethyl)-3-pentanoylamino-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.2 (1H, br s), 10.16 (1H, br s), 7.85-7.75 (4H, m), 7.53 (1H, d, *J*=7.4 Hz), 7.40-7.26 (5H, m), 7.25-7.13 (2H, m), 7.00 (1H, d, *J*=8.4 Hz), 6.06 (2H, s), 6.04 (2H, s), 3.83 (2H, s), 2.41 (2H, t, *J*=7.4 Hz), 1.75-1.58 (2H, m), 1.51-1.30 (2H, m), 0.95 (3H, t, *J*=7.2 Hz).

Example 90

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-(3-phenylacryloylamino)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.52 (1H, br s), 10.1 (1H, s), 8.11 (1H, s), 7.79 (1H, d, *J*=8.5 Hz), 7.74-7.38 (9H, m), 7.36-7.18 (3H, m), 7.16-7.03 (2H, m), 7.01-6.94 (1H, m), 5.98 (2H, s).

Example 91

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-(2,2-dimethylpropionyl-amino)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.8-13.2 (1H, s), 9.51 (1H, s), 8.06 (1H, s), 7.81 (1H, d, *J*=8.6 Hz), 7.63-7.51 (3H, m), 7.37-7.13 (4H, m), 7.01-6.93 (1H, m), 5.96 (2H, s), 1.31 (9H, s).

Example 92

3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-6-(3,5-difluorophenyl)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 10.3 (1H, s), 8.12-8.06 (3H, m), 7.80 (1H, d, *J*=8.6 Hz), 7.67-7.55 (5H, m), 7.37-7.14 (4H, m), 7.01-6.96 (1H, m), 5.99 (2H, s).

Example 93

1-(3-Chlorobenzyl)-6-(2-isopropoxyphenyl)-3-pentanoylaminoindole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.2-13.5 (1H, br s) 10.4 (1H, br s) 7.85 (1H, d, *J*=8.5 Hz) 7.56 (1H, s) 7.38-7.24 (4H, m) 7.21 (1H, d, *J*=8.4 Hz) 7.12-6.96 (4H, m) 5.93 (2H, s) 4.51 (1H, septet, *J*=6.1 Hz) 2.41 (2H, t, *J*=7.3 Hz) 1.76-1.58 (2H, m) 1.51-1.31 (2H, m), 1.05 (6H, d, *J*=6.1 Hz), 0.95 (3H, t, *J*=7.5 Hz).

Example 94

1-(3-Chlorobenzyl)-6-(2-isopropoxyphenyl)-3-phenylindole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 12.99 (1H, br s), 7.71 (1H, s), 7.56-7.26 (11H, m), 7.24-7.20 (1H, m), 7.13-6.97 (3H, m), 5.89 (2H, s), 4.54 (1H, septet, *J*=6.0 Hz), 1.07 (6H, d, *J*=6.0 Hz).

Example 95

3-[(Biphenyl-4-carbonyl)amino]-1-(3-chlorobenzyl)-6-(2-isopropoxyphenyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 11.0-11.3 (1H, br s), 8.22-8.14 (2H, m), 7.97 (1H, d, *J*=8.4 Hz), 7.93-7.86 (2H, m), 7.84-7.78 (2H, m), 7.65 (1H, s), 7.60-7.44 (3H, m), 7.42-7.24 (5H, m), 7.16-6.98 (4H, m), 5.97 (2H, s), 4.53 (1H, septet, *J*=6.0 Hz), 1.07 (6H, d, *J*=6.0 Hz).

Example 96

1-(3-Chlorobenzyl)-6-(4-isopropoxyphenyl)-3-pentanoylaminoindole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.3 (1H, br s), 9.65 (1H, s), 7.81 (1H, s), 7.70-7.92 (3H, m), 7.42 (1H, dd, *J*=8.5, 1.1 Hz), 7.37-7.25 (2H, m), 7.12-6.94 (4H, m), 5.92 (2H, s), 4.68 (1H, septet, *J*=6.0 Hz), 2.42 (2H, t, *J*=7.4 Hz), 1.74-1.56 (2H, m), 1.51-1.29 (2H, m), 1.26 (6H, d, *J*=6.0 Hz), 0.95 (3H, t, *J*=7.2 Hz).

Example 97

1-(3-Chlorobenzyl)-6-(4-isopropoxyphenyl)-3-phenylindole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 12.98 (1H, br s), 7.88 (1H, s), 7.70-7.61 (2H, m), 7.56-7.27 (9H, m), 7.26-7.22 (1H, m), 7.08-6.97 (3H, m), 5.97 (2H, s), 4.68 (1H, septet, *J*=6.0 Hz), 1.30 (6H, d, 6.0 Hz).

Example 98

1-(3-Chlorobenzyl)-3,6-bis-(4-isopropoxyphenyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 12.95 (1H, br s), 7.85 (1H, s), 7.69-7.60 (2H, m), 7.54 (1H, d, *J*=8.6 Hz), 7.47-7.27 (5H, m), 7.24-7.20 (1H, m), 7.06-6.96 (5H, m), 5.95 (2H, s), 4.69 (1H, septet, *J*=6.0 Hz), 4.68 (1H, septet, *J*=6.0 Hz), 1.34 (6H, d, *J*=6.0 Hz) 1.30 (6H, d, *J*=6.0 Hz).

Example 99

1-(3-Chlorobenzyl)-6-(3-isopropoxyphenyl)-3-phenylindole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.08 (1H, br s), 7.94 (1H, s), 7.58-7.31 (10H, m), 7.30-7.21 (3H, m), 7.08-7.02 (1H, m), 6.97-6.89 (1H, m), 5.99 (2H, s), 4.73 (1H, septet, *J*=6.0 Hz), 1.31 (6H, d, *J*=6.0 Hz).

Example 100

1-(3-Chlorobenzyl)-3-(3-isopropoxyphenyl)-6-(4-isopropoxyphenyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 7.81 (1H, s), 7.64-7.57 (2H, m), 7.51 (1H, d, *J*=8.5 Hz), 7.44-7.38 (1H, m), 7.34 (1H, dd, *J*=8.0, 2.0 Hz), 7.30-7.24 (2H, m), 7.22-7.19 (1H, m), 7.05-6.93 (5H, m), 6.88 (1H, dd, *J*=8.0, 2.1 Hz), 5.89 (2H, s), 4.63 (1H, septet, *J*=6.0 Hz), 4.61 (1H, septet, *J*=6.0 Hz), 1.28 (6H, d, *J*=6.0 Hz), 1.26 (6H, d, *J*=6.0 Hz).

Example 101

1-(3-Chlorobenzyl)-6-(3-isopropoxyphenyl)-3-pentanoylaminoindole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.1 (1H, br s), 9.64 (1H, br s), 7.84 (1H, s), 7.64 (1H, d, *J*=8.5 Hz), 7.41 (1H, d, *J*=8.5 Hz), 7.36 (1H, d, *J*=7.8 Hz), 7.31-7.17 (4H, m), 7.12-7.08 (1H, m), 6.95-6.85 (2H, m), 5.91

(2H, s), 4.70 (1H, septet, *J*=6.0 Hz), 2.38 (2H, t, *J*=7.3 Hz), 1.70-1.53 (2H, m), 1.47-1.27 (2H, m), 1.27 (6H, d, *J*=6.0 Hz), 0.91 (3H, t, *J*=7.2 Hz).

Example 102

1-(3-Chlorobenzyl)-6-(4-isopropoxyphenyl)-3-(2-isopropoxyphenyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 12.67 (1H, br s), 7.81 (1H, s), 7.67-7.59 (2H, m), 7.43-7.26 (6H, m), 7.19-7.15 (1H, m), 7.13-6.97 (5H, m), 5.96 (2H, s), 4.67 (1H, septet, *J*=6.0 Hz), 4.46 (1H, septet, *J*=6.0 Hz), 1.30 (6H, d, *J*=6.0 Hz), 1.13 (6H, d, *J*=6.0 Hz).

Example 103

1-(3-Chlorobenzyl)-3-pentanoylamino-5-[4-(trifluoromethyl)phenyl]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.3 (1H, br s), 9.7 (1H, br s), 8.93 (1H, s), 7.90-7.75 (4H, m), 7.73-7.63 (2H, m), 7.35-7.24 (2H, m), 7.13-6.04 (1H, m), 7.00-6.92 (1H, m), 5.84 (2H, s), 2.40 (2H, t, *J*=7.5 Hz), 1.71-1.51 (2H, m), 1.47-1.26 (2H, m), 0.91 (3H, t, *J*=7.2 Hz).

Example 104

1-(3-Chlorobenzyl)-5-[4-(methylthio)phenyl]-3-pentanoylaminoindole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 10.9-10.7 (1H, br s), 8.21 (1H, s), 7.59-7.44 (4H, m), 7.36-7.20 (4H, m), 7.12 (1H, s), 7.06-6.97 (1H, m), 5.96 (2H, s), 2.48 (3H, s, overlapped with DMSO), 2.37 (2H, t, *J*=7.4 Hz), 1.71-1.51 (2H, m), 1.46-1.24 (2H, m), 0.90 (3H, t, *J*=7.2 Hz).

Example 105

1-(3-Chlorobenzyl)-3-(4-methoxybenzoylamino)-5-[4-(methylthio)phenyl]-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 12.0-11.8 (1H, br s), 8.47 (1H, s), 8.07-7.96 (2H, m), 7.63-7.47 (4H, m), 7.36-7.22 (4H, m), 7.17 (1H, s), 7.12-7.00 (3H, m), 6.03 (2H, s), 3.80 (3H, s), 2.48 (3H, s, overlapped with DMSO).

Example 106

3-[(Biphenyl-4-carbonyl)amino]-5-(4-*tert*-butylphenyl)-1-(3-chlorobenzyl)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 10.4-10.3 (1H, br s), 8.19-8.09 (2H, m), 7.93 (1H, s), 7.89-7.81 (2H, m), 7.80-7.61 (4H, m), 7.62-7.35 (7H, m), 7.34-7.25 (2H, m), 7.18-7.13 (1H, m), 7.05-6.97 (1H, m), 5.88 (2H, s), 1.28 (9H, s).

Example 107

3-(3-Amino-4-methylbenzoylamino)-1-(3-chlorobenzyl)-5-[4-(methylsulfonyl)phenyl]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 10.2-10.1 (1H, br s), 8.16 (1H, s), 8.01-7.86 (4H, m), 7.75-7.72 (2H, m), 7.37-7.24 (3H, m), 7.16-7.11 (2H, m), 7.09-6.93 (2H, m), 5.58 (2H, s), 3.22 (3H, s), 2.11 (3H, s).

Example 108

5-(4-*tert*-Butylphenyl)-1-(3-chlorobenzyl)-3-(4-isopropoxyphenyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 7.64 (1H, s), 7.60-7.34 (8H, m), 7.33-7.22 (3H, m), 7.16-7.06 (1H, m), 6.99-6.89 (2H, m), 5.80 (2H, s), 4.62 (1H, septet, J=6.0 Hz), 1.28 (6H, d, J=6.0 Hz), 1.27 (9H, s).

Example 109

1-(3-Chlorobenzyl)-6-(4-isopropoxyphenyl)-3-(4-methoxybenzoylamino)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.3 (1H, br s), 10.16 (1H, s), 8.09-8.00 (2H, m), 7.86-7.77 (2H, m), 7.70-7.62 (2H, m), 7.42 (1H, d, *J*=8.5 Hz), 7.38-7.24 (2H, m), 7.16-7.10 (2H, m), 7.07 (1H, s), 7.04-6.96 (3H, m), 5.95 (2H, s), 4.67 (1H, septet, *J*=6.1 Hz), 3.86 (3H, s), 1.28 (6H, d, *J*=6.1 Hz).

Example 110

N-[1-(3-Chlorobenzyl)-2-hydroxymethyl-6-(4-isopropoxyphenyl)indol-3-yl]-4-methoxybenzamide

$LiAlH_4$ (6.4 mg, 0.17 mmol) was added to a solution of 1-(3-chlorobenzyl)-6-(4-isopropoxyphenyl)-3-(4-methoxybenzoylamino)indole-2-carboxylic acid ethyl ester, prepared in accordance with the procedure described in Example 7(a), (100 mg, 0.17 mmol) in THF (5 mL) at 0°C. After stirring for 1 h another portion of $LiAlH_4$ (6.4 mg, 0.17 mmol) was added and the stirring was continued at room temperature for 1 h. The mixture was acidified to pH 2 with HCl (aq., 4M), diluted with water and extracted with EtOAc. The combined extracts were washed with water, brine, and dried over Na_2SO_4 and concentrated. Purification of the residue by chromatography gave the title compound (59 mg, 64%).

^{1}H NMR (200 MHz, DMSO-d_6): δ 9.85 (1H, s), 8.08-7.99 (2H, m), 7.59 (1H, s), 7.57-7.50 (2H, m), 7.44 (1H, d, *J*=8.4 Hz), 7.38-7.23 (3H, m), 7.21-7.16 (1H, m), 7.14-7.02 (3H, m), 6.99-6.90 (2H, m), 5.63 (2H, s), 5.20 (1H, t, *J*=5.1 Hz), 4.62 (1H, septet, *J*=6.0 Hz), 4.54 (2H, d, *J*=5.1 Hz), 3.83 (3H, s), 1.25 (6H, d, *J*=6.0 Hz).

The following Examples 111 to 130 were prepared by analogous techniques to those described herein.

Example 111

5-(4-*tert*-Butylphenyl)-1-(3-chlorobenzyl)-3-[4-(trifluoromethoxy)phenyl]-indole-2-carboxylic acid

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.69-7.60 (2H, m), 7.58-7.30 (9H, m), 7.25-7.12 (3H, m), 7.03-6.94 (1H, m), 5.83 (2H, s), 1.34 (9H, s).

Example 112

3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-5-[4-(trifluoromethyl)-phenyl]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 12.4-12.2 (1H, br s), 8.53 (1H, s), 8.10-7.99 (2H, m), 7.92-7.72 (4H, m), 7.64-7.56 (4H, m), 7.34-7.15 (3H, m), 7.10-7.01 (1H, m), 6.04 (2H, s).

Example 113

5-(4-*tert*-Butylphenyl)-1-(3-chlorobenzyl)-3-[4-(methylthio)phenyl]indole-2-carboxylic acid

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.73-7.69 (1H, m), 7.67-7.58 (1H, m), 7.54-7.30 (9H, m), 7.25-7.13 (3H, m), 7.02-6.94 (1H, m), 5.81 (2H, s), 2.56 (3H, s), 1.35 (9H, s).

Example 114

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-[4-(dimethylamino)benzoyl-amino]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.6-13.4 (1H, br s), 10.08 (1H, br s), 8.05 (1H, s), 7.95-7.87 (3H, m), 7.59-7.48 (3H, m), 7.31-7.11 (4H, m), 6.97-6.91 (1H, m), 6.82-6.74 (2H, m), 5.96 (2H, br s), 3.00 (6H, s).

Example 115

3-(4-*tert*-Butylbenzoylamino)-1-(3-chlorobenzyl)-6-(3,5-difluorophenyl)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.6-13.4 (1H, br s), 10.24 (1H, s), 8.11 (1H, s), 8.03-7.96 (2H, m), 7.84 (1H, d, *J*=8.6 Hz), 7.62-7.54 (5H, m), 7.37-7.13 (4H, m), 7.00-6.95 (1H, m), 5.99 (2H, s), 1.34 (9H, s).

Example 116

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-(3,5-dimethoxybenzoyl-amino)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.6-13.3 (1H, br s), 10.26 (1H, s), 8.09 (1H, s), 7.82 (1H, d, *J*=8.6 Hz), 7.60-7.49 (3H, m), 7.31-7.10 (6H, m), 7.00-6.93 (1H, m), 6.73-6.69 (1H, m), 5.97 (2H, s), 3.81 (6H, s).

Example 117

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-[2-(3,3,5,5-tetramethylcyclo-hexyl)acetylamino]-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.4-13.3 (1H, br s), 9.68 (1H, s), 8.04 (1H, s), 7.67 (1H, d, *J*=8.5 Hz), 7.59-7.50 (3H, m), 7.30-7.14 (3H, m), 7.10-7.05 (1H, m), 6.96-6.89 (1H, m), 5.91 (2H, s), 2.25-2.19 (2H, m), 1.55-1.45 (2H, m), 1.25-0.75 (5H, m), 0.99 (6H, s), 0.86 (6H, s).

Example 118

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-[2-(3,3,5,5-tetramethylcyclo-hexyl)acetylamino]indole-2-carboxylic acid sodium salt

^{1}H NMR (200 MHz, DMSO-d_6): δ 12.09 (1H, s) 7.35 (1H, d, *J*=8.5 Hz) 7.78 (1H, s) 7.51-7.43 (2H, m) 7.34 (1H, d, *J*=8.5 Hz) 7.27-7.16 (3H, m) 7.15-7.07 (2H, m) 6.17 (2H, s) 2.22-2.16 (2H, m) 1.54-1.44 (2H, m) 1.27-1.18 (1H, m) 1.06-0.73 (4H, m) 1.00 (6H, s), 0.87 (6H, s).

Example 119

1-(3-Chlorobenzyl)-3-(3-cyclohexylpropionylamino)-6-(3,5-difluorophenyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.4-13.3 (1H, br s), 9.63 (1H, s), 8.04 (1H, s), 7.66 (1H, d, *J*=8.6 Hz), 7.58-7.48 (3H, m), 7.30-7.14 (3H, m), 7.08-7.05 (1H, m), 6.95-6.89 (1H, m), 5.91 (2H, s), 2.43-2.34 (2H, m), 1.79-1.48 (7H, m), 1.30-1.10 (4H, m), 0.98-0.81 (2H, m).

Example 120

3-(4-Butylbenzoylamino)-1-(3-chlorobenzyl)-6-(3,5-difluorophenyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.6-13.3 (1H, br s), 10.21 (1H, s), 8.09 (1H, s), 7.98-7.92 (2H, m), 7.82 (1H, d, *J*=8.5 Hz), 7.61-7.51 (3H, m), 7.38-7.33 (2H, m), 7.31-7.11 (4H, m), 6.98-6.93 (1H, m), 5.96 (2H, s), 2.69-2.62 (2H, m), 1.66-1.51 (2H, m), 1.40-1.22 (2H, m), 0.89 (3 H, t, *J*=7.2 Hz).

Example 121

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-(4-isopropylbenzoylamino)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.6-13.3 (1H, br s), 10.26 (1H, br s), 8.08 (1H, m), 8.00-7.94 (2H, m), 7.83 (1H, d, *J*=8.6 Hz), 7.60-7.50 (3H, m), 7.43-7.37 (2H, m), 7.32-7.11 (4H, m), 7.00-6.93 (1H, m), 5.97 (2H, s), 2.98 (1H, septet, *J*=7.4 Hz), 1.24 (6H, d, *J*=7.4 Hz).

Example 122

3-[(1-Adamantylcarbonyl)amino]-1-(3-chlorobenzyl)-6-(3,5-difluorophenyl)indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.8-13.2 (1H, br s), 9.45 (1H, s), 8.03 (1H, s), 7.79 (1H, d, *J*=8.6 Hz), 7.58-7.46 (3H, m), 7.32-7.08 (4H, m), 6.96-

6.88 (1H, m), 5.92 (2H, s), 2.04-2.00 (3H, m), 1.96-1.95 (6H, m), 1.72-1.69 (6H, m).

Example 123

3-[(1-Adamantylcarbonyl)amino]-1-(3-chlorobenzyl)-6-(3,5-difluorophenyl)indole-2-carboxylic acid sodium salt

^{1}H NMR (200 MHz, DMSO-d_6): δ 12.34 (1H, s), 8.37 (1H, d, J=8.6 Hz), 7.74 (1H, s), 7.48-7.41 (2H, m), 7.31-7.16 (4H, m), 7.14-7.04 (2H, m), 6.16 (2H, s), 2.05-1.99 (3H, m), 1.96-1.91 (6H, m), 1.73-1.68 (6H, m).

Example 124

1-(3-Chlorobenzyl)-6-(3,5-difluorophenyl)-3-[4-(trifluoromethoxy)benzoylamino]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.6-13.3 (1H, br s), 10.38 (1H, s), 8.19-8.09 (3H, m), 7.78 (1H, d, J=8.6 Hz), 7.58-7.52 (5H, m), 7.32-7.11 (4H, m), 6.99-6.94 (1H, m), 5.97 (2H, s).

Example 125

1-(3-Chlorobenzyl)-3-(4-cyanobenzoylamino)-6-(3,5-difluorophenyl)-indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.3 (1H, br s), 10.50 (1H, s), 8.22-8.15 (2H, m), 8.12-8.01 (3H, m), 7.77 (1H, d, J=8.6 Hz), 7.60-7.51 (3H, m), 7.35-7.10 (4H, m), 7.00-6.94 (1H, m), 5.97 (2H, s).

Example 126

6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-[(3,5-dimethyladamant-1-ylcarbonyl)amino]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.4 (1H, br s), 9.51 (1H, s), 7.81 (1H, s), 7.77 (1H, d, J=8.8 Hz), 7.66-7.58 (2H, m), 7.42-7.36 (1H, m), 7.29-7.23 (4H, m), 7.10-7.09 (1H, m), 6.96-6.91 (1H, m), 5.90 (2H, s), 2.60 (2H,

t, *J*=7.2 Hz), 2.15-2.08 (1H, m), 1.81-1.78 (2H, m), 1.62-1.48 (6H, m), 1.40-1.24 (6H, m), 1.19-1.16 (2H, m) 0.89 (3H, t, *J*=7.2 Hz), 0.85 (6H, s).

Example 127

6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-[(3,5-dimethyladamant-1-ylcarbonyl)amino]indole-2-carboxylic acid sodium salt

^{1}H NMR (200 MHz, DMSO-d_6): δ 12.30 (1H, s), 8.30 (1H, d, *J*=8.5 Hz), 7.57-7.50 (3H, m), 7.26-7.15 (6H, m), 7.11-7.05 (1H, m), 6.13 (2H, s), 2.57 (2H, t, *J*=7.2 Hz), 2.15-2.08 (1H, m), 1.79-1.74 (2H, m), 1.59-1.47 (6H, m), 1.39-1.25 (6H, m), 1.19-1.15 (2H, m) 0.88 (3H, t, *J*=7.2 Hz), 0.85 (6H, s).

Example 128

6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-[4-(2,5-dimethylpyrrol-1-yl)benzoylamino]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.4-13.2 (1H, br s), 10.48 (1H, br s), 8.20-8.12 (2H, m), 7.88 (1H, s), 7.81 (1H, d, *J*=8.5 Hz), 7.69-7.61 (2H, m), 7.48-7.42 (3H, m), 7.32-7.24 (4H, m), 7.16-7.13 (1H, m), 7.04-6.98 (1H, m), 5.96 (2H, br s), 5.83 (2H, s), 2.60 (2H t, *J*=7.2 Hz), 2.01 (6H, s), 1.63-1.49 (2H, m), 1.39-1.22 (2H, m), 0.89 (3H, t, *J*=7.2 Hz).

Example 129

6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-[4-(trifluoromethoxy)benzoylamino]indole-2-carboxylic acid

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.3 (1H, br s), 10.37 (1H, s), 8.20-8.14 (2H, m), 7.88 (1H, s), 7.76 (1H, d, *J*=7.6 Hz), 7.66-7.60 (2H, m), 7.59-7.53 (2H, m), 7.47-7.41 (1H, m), 7.32-7.23 (4H, m), 7.15-7.11 (1H, m), 7.02-6.96 (1H, m), 5.95 (2H, s), 2.60 (2H, t, *J*=7.2 Hz), 1.63-1.49 (2H, m), 1.39-1.21 (2H, m), 0.89 (3H, t, *J*=7.2 Hz).

Example 130

6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-[4-(trifluoromethoxy)benzoyl-amino]indole-2-carboxylic acid sodium salt

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.67 (1H, s), 8.51 (1H, d, *J*=7.6 Hz), 8.18-8.12 (2H, m), 7.61-7.51 (5H, m), 7.31-7.18 (6H, m), 7.14-7.08 (1H, m), 6.19 (2H, s), 2.57 (2H, t, *J*=7.2 Hz), 1.62-1.47 (2H, m), 1.35-1.21 (2H, m), 0.88 (3H, t, *J*=7.2 Hz).

Example 131

6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-(4-isopropoxybenzoylamino)-indole-2-carboxylic acid

(a) 6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-(4-isopropoxybenzoylamino)-indole-2-carboxylic acid ethyl ester

A mixture of 3-amino-6-(4-butylphenyl)-1-(3-chlorobenzyl)indole-2-carboxylic acid ethyl ester (250 mg, 540 nmol), 4-isopropoxybenzoyl chloride (162 mg, 810 nmol), DMAP (33 mg, 270 nmol), triethylamine (229 µL, 1.63 mmol) and dry MeCN (2 mL) was stirred at room temperature under argon for 18h and then heated at 80°C for 10 min, at 100°C for 5 min and finally at 120°C for 10 min using microwave irradiation. The mixture was poured into HCl (1M) and extracted with EOAc. The combined extracts were washed with $NaHCO_3$, dried with Na_2SO_4 and concentrated. The residue was crystallised from EOAc/benzene to yield the title compound (150 mg, 44%).

(b) 6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-(4-isopropoxybenzoylamino)-indole-2-carboxylic acid

The title compound (45 mg, 32%) was prepared by hydrolysis of 6-(4-butylphenyl)-1-(3-chlorobenzyl)-3-(4-isopropoxybenzoylamino)indole-2-

carboxylic acid ethyl ester (see Example 131(a)) under conditions as hereinbefore described, for example at 90°C for 10 min in 1,4-dioxane.

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.3 (1H, br s), 10.14 (1H, s), 8.03-7.95 (2H, m), 7.86 (1H, s), 7.80 (1H, d, *J*=7.6 Hz), 7.67-7.60 (2H, m), 7.46-7.39 (1H, m), 7.31-7.23 (4H, m), 7.14-7.11 (1H, m), 7.08-7.04 (2H, m), 7.01-6.95 (1H, m), 5.94 (2H, s), 4.74 (1H, septet, *J*=6.0 Hz), 2.60 (2H, t, *J*=7.2 Hz), 1.64-1.49 (2H, m), 1.36-1.25 (2H, m), 1.30 (6H, d, *J*=6.0 Hz), 0.89 (3H, t, *J*=7.2 Hz).

Example 132

6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-(3-isopropoxybenzoylamino)-indole-2-carboxylic acid

The title compound was prepared in accordance with the procedures described herein.

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.3 (1H, br s), 10.25 (1H, s), 7.87 (1H, s), 7.75 (1H, d, *J*=8.5 Hz), 7.67-7.54 (4H, m), 7.47-7.37 (2H, m), 7.34-7.22 (4H, m), 7.16-7.10 (2H, m), 7.02-6.95 (1H, m), 5.94 (2H, s), 4.71 (1H, septet, *J*=6.0 Hz), 2.60 (2H, t, *J*=7.2 Hz), 2.15-2.08 (2H, m), 1.36-1.21 (2H, m), 1.29 (6H, d, *J*=6.0 Hz), 0.88 (3H, t, *J*=7.2 Hz).

Example 133

6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-(3-isopropoxybenzoylamino)-indole-2-carboxylic acid sodium salt

The title compound was prepared in accordance with the procedures described herein.

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.58 (1H, s) 8.52 (1H, d, J=8.6 Hz) 7.60-7.51 (5H, m) 7.46-7.38 (1H, m) 7.29-7.17 (6H, m) 7.14-7.07 (2H, m) 6.18 (2H, s) 4.69 (1H, septet, *J*=6.0 Hz) 2.58 (2H, t, *J*=7.2 Hz) 1.63-1.49 (2H, m) 1.35-1.24 (2H, m) 1.30 (6H, d, *J*=6.0 Hz), 0.88 (3H, t, *J*=7.2 Hz).

Example 134

6-(4-Carboxyphenyl)-3-(4-chlorobenzoylamino)-1-(3-chlorobenzyl)indole-2-carboxylic acid

The title compound was prepared in accordance with the procedures described herein.

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.6-12.8 (2H, br s), 10.37 (1H, s), 8.13-7.99 (5H, m), 7.94-7.86 (2H, m), 7.82 (1H, d, *J*=8.6 Hz), 7.68-7.61 (2H, m), 7.59-7.51 (1H, m), 7.38-7.24 (2H, m), 7.17-7.11 (1H, m), 7.04-6.95 (1H, m), 5.99 (2H, s).

Example 135

3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-6-(4-hydroxymethylphenyl)-indole-2-carboxylic acid

(a) 3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-6-(4-hydroxymethyl-phenyl)indole-2-carboxylic acid ethyl ester

1M BH_3xTHF (1M, 200μL, 0.20 mmol) was added to a stirred solution of 6-(4-carboxyphenyl)-3-(4-chlorobenzoylamino)-1-(3-chlorobenzyl)indole-2-carboxylic acid ethyl ester, prepared by analogous techniques to those described hereinbefore, (120 mg, 0.20 mmol) in THF (5 mL) at –5 °C. The temperature of the mixture was allowed to reach room temperature and stirring was continued for 12 h whereafter another portion of 1M BH_3xTHF (1M, 200μL, 0.20 mmol) was added. The mixture was stirred for 8 h at room temperature and poured into AcOH (aq., 50%, 20 mL) and stirred for 1 h. The mixture was extracted with EtOAc and the combined extracts were washed with H_2O and brine, dried over Na_2SO_4 and concentrated. Purification of the residue by chromatography gave the sub-title compound (90 mg, 78 %).

(b) 3-(4-Chlorobenzoylamino)-1-(3-chlorobenzyl)-6-(4-hydroxymethyl-phenyl)indole-2-carboxylic acid

The title compound was prepared by hydrolysis of 3-(4-chlorobenzoyl-amino)-1-(3-chlorobenzyl)-6-(4-hydroxymethylphenyl)indole-2-carboxylic acid ethyl ester in accordance with the procedure in Example 2(b) (NaOH (1M), MeCN, 80 °C, 20 min).

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.2 (1H, br s), 10.35 (1H, s), 8.13-8.04 (2H, m), 7.92 (1H, s), 7.79 (1H, d, *J*=8.4 Hz), 7.70-7.57 (4H, m), 7.51-7.25 (5H, m), 7.17-7.12 (1H, m), 7.04-6.96 (1H, m), 5.98 (2H, s), 5.14-5.34 (1H, m), 4.62-4.54 (2H, m).

Example 136

6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-[3-(2,5-dimethylpyrrol-1-yl)benz-oylamino]indole-2-carboxylic acid

(a) 6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-(3-nitrobenzamido)indole-2-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 131(a) using 3-nitrobenzoyl chloride (room temperature overnight, and then 90°C for 10 min, 110°C for 10 min and finally 130°C for 20 min).

(b) 3-(3-Aminobenzamido)-6-(4-butylphenyl)-1-(3-chlorobenzyl)indole-2-carboxylic acid ethyl ester

6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-(3-nitrobenzamido)indole-2-carboxylic acid ethyl ester (235 mg, 0.39 mmol; see Example 136(a)) was hydrogenated at ambient pressure and temperature using palladium on charcoal (10%, 62 mg) in EtOAc for 6 h, then filtered through Celite®. The filtrate was concentrated and the residue was crystallised from EtOAc/benzene to yield the sub-title compound (140 mg, 62%).

(c) 6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-(3-(2,5-dimethylpyrrol-1-yl)-benzamido)indole-2-carboxylic acid ethyl ester

A mixture of 3-(3-aminobenzamido)-6-(4-butylphenyl)-1-(3-chlorobenzyl)-indole-2-carboxylic acid ethyl ester (140 mg, 240 nmol; see Example 136(b)), hexane-2,5-dione (189 μL, 1.21 mmol), *p*-toluenesulfonic acid (50 ng, 0.24 nmol) and toluene (1 mL) was stirred at room temperature for 1 h and then heated at 70°C for 20 min using microwave irradiation. The mixture was diluted with EOAc, washed with Na_2CO_3 (aq., sat.), dried over Na_2SO_4, and concentrated. The residue was crystallised from petroleum ether/benzene to yield the sub-title compound (97 mg, 61%).

(d) 6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-[3-(2,5-dimethylpyrrol-1-yl)-benzoylamino]indole-2-carboxylic acid

The title compound was prepared by hydrolysis of 6-(4-butylphenyl)-1-(3-chlorobenzyl)-3-[3-(2,5-dimethylpyrrol-1-yl)benzoylamino]indole-2-carboxylic acid ethyl ester (see Example 136(c)) in accordance with the procedure described in Example 2(b) (2M KOH, dioxane, 70 °C, 10 min, then 80 °C 20 min and finally 90 °C 10 min).

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.3 (1H, br s), 10.8-10.4 (1H, br s), 8.14-8.08 (1H, m), 7.93-7.80 (3H, m), 7.73-7.69 (1H, m), 7.66-7.60 (2H, m), 7.55-7.49 (1H, m), 7.43 (1H, d, *J*=8.5 Hz), 7.31-7.23 (4H, m), 7.13-7.11 (1H, m), 7.02-6.96 (1H, m), 5.96 (2H, s), 5.83 (2H, s), 2.59 (2H, t, *J*=7.2 Hz), 2.00 (6H, s), 1.63-1.49 (2H, m), 1.39-1.21 (2H, m), 0.88 (3H, t, *J*=7.2 Hz).

Example 137

6-(4-Butylphenyl)-1-(3-chlorobenzyl)-3-[3-(2,5-dimethylpyrrol-1-yl)benzoylamino]indole-2-carboxylic acid sodium salt

The title compound was prepared in accordance with the procedures described herein.

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.91 (1H, br s), 8.57 (1H, d, *J*=8.5 Hz), 8.11-8.07 (1H, m), 7.83-7.81 (1H, m), 7.74-7.66 (1H, m), 7.61-7.54 (3H, m), 7.52-7.76 (1H, m), 7.31-7.19 (6H, m), 7.14-7.09 (1H, m), 6.19 (2H, s), 5.84 (2H, s), 2.59 (2H, t, *J*=7.2 Hz), 2.03 (6H, s), 1.64-1.49 (2H, m), 1.38-1.22 (2H, m), 0.89 (3H, t, *J*=7.2 Hz).

Example 138

3-(4-Chlorobenzoylamino)-1-(4-chlorobenzyl)-5-[4-(trifluoromethyl)-phenyl]-indole-2-carboxylic acid

The title compound was prepared in accordance with the procedures described herein.

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5-13.1 (1H, br s), 10.6-10.4 (1H, br s), 8.12-8.00 (3H, m), 7.93-7.84 (2H, m), 7.82-7.68 (4H, m), 7.68-7.57 (2H, m), 7.41-7.30 (2H, m), 7.13-7.03 (2H, m), 5.89 (2H, m).

Example 139

3-[Acetyl-(4-methoxybenzyl)amino]-1-(3-chlorobenzyl)-5-(4-isopropoxy-phenyl)indole-2-carboxylic acid

(a) 3-Bromo-5-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

A solution of NBS (0.904 5.082 mmol) in acetone (10 mL) was added dropwise to a solution of 5-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester, prepared in accordance with Example 1(a) from 5-bromoindole-carboxylic acid ethyl ester and 4-isopropoxyphenylboronic acid, (1.5 g, 4.62 mmol) in acetone (35 mL) at room temperature. After 2.5 h an additional portion of NBS (164 mg, 0.92 mmol) was added and temperature of the mixture was increased to 45 °C. After 1.5 h the mixture was cooled to room temperature, poured into $Na_2S_2O_3$ (aq., 10%) and extracted with EtOAc. The extract was washed with $Na_2S_2O_3$ (aq., 10%), $NaHCO_3$ (aq., sat) and

brine, dried over Na_2SO_4 and concentrated. The residue was crystallised from EtOH to give the sub-title compound (1.63 g, 88 %).

(b) 1-(3-Chlorobenzyl)-5-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 1(c) from 3-bromo-5-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (1.0 g, 2.5 mmol, see step (a) above) and 3-chlorobenzylchloride (0.604 g, 3.75 mmol). Yield 0.784 g (60 %).

(c) 1-(3-Chlorobenzyl)-5-(4-isopropoxyphenyl)-3-[(4-methoxybenzyl)-amino]indole-2-carboxylic acid ethyl ester

4-Methoxybenzylamine (60 µL, 0.46 mmol) was added to a mixture of 1-(3-chlorobenzyl)-5-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (200 mg, 0.38 mmol), $Pd_2(dba)_3$ (17.4 mg, 0.019 mmol), BINAP (35.5 mg, 0.057 mmol), Cs_2CO_3 (173 mg, 0.53 mmol) and anhydrous toluene (10 mL). The mixture was stirred at 120°C for 24 h, cooled to room temperature and diluted with Et_2O. The mixture was filtered through Celite® and the filter cake washed with Et_2O. The combined filtrates were concentrated and the residue purified by chromatography to yield the sub-title compound (0.213 g, 96 %).

(d) 3-[Acetyl-(4-methoxybenzyl)amino]-1-(3-chlorobenzyl)-5-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

Acetyl chloride (24 µL, 0.34 mmol) was added at room temperature to a solution of 1-(3-chlorobenzyl)-5-(4-isopropoxyphenyl)-3-[(4-methoxybenzyl)amino]indole-2-carboxylic acid ethyl ester (200 mg, 0.34 mmol) in dry toluene (2mL). The mixture was stirred at 70 °C for 1 h, allowed to cool to room temperature, diluted with EtOAc and washed with $NaHCO_3$ (aq., sat.),

brine and finally dried over Na_2SO_4. Concentration and purification by chromatography gave the sub-title compound (0.136 g, 64 %).

(e) 3-[Acetyl-(4-methoxybenzyl)amino]-1-(3-chlorobenzyl)-5-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared by hydrolysis of 3-[acetyl-(4-methoxybenzyl)amino]-1-(3-chlorobenzyl)-5-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (136 mg, 0.217 mmol; see step (d) above), in accordance with the procedure in Example 1(e) (NaOH (aq.), dioxane, 80°C, 1 h). Yield: 93 mg (72 %).

^{1}H NMR (200 MHz, DMSO-d_6): δ 13.7-13.3 (1H, br s), 7.55-7.40 (2H, m), 7.35-7.24 (4H, m), 7.15-7.06 (2H, m), 7.02-6.84 (5H, m), 6.80-6.71 (2H, m), 5.86 (2H, s), 5.34 (1H, d, *J*=14.0 Hz), 4.61 (1H, septet *J*=6.0 Hz), 4.21 (1H, d, *J*=14.0 Hz), 3.64 (3H, s), 1.72 (3H, s), 1.26 (6H, d, *J*=6.0 Hz).

Example 140

1-(3-Chlorobenzyl)-3-{(4-chlorobutyryl)-[2-(4-fluorophenyl)ethyl]amino}-5-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with the procedure in Example 139(c)-(e) from 1-(3-chlorobenzyl)-5-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester, 2-(4-fluorophenyl)ethylamine and 4-chlorobutyryl chloride.

^{1}H NMR (200 MHz, DMSO-d_6): δ 7.54-7.36 (5H, m), 7.34-6.87 (10H, m), 6.05 (1H, d, *J*=16.0 Hz), 5.87 (1H, d, *J*=16.0 Hz), 4.60 (1H, septet, *J*=6.0 Hz), 4.19-3.96 (1H, m), 3.82-3.61 (1H, m), 3.22 (2H, t, *J*=6.4 Hz), 2.85-2.70 (2H, m), 2.37-2.10 (1H, m), 2.07-1.85 (1H, m), 1.67-1.44(2H, m), 1.25 (6H, d, *J*=6.0 Hz).

Example 141

1-(3-Chlorobenzyl)-3-{(6-chloropyridine-3-carbonyl)-[2-(4-fluorophenyl)-ethyl]amino}-5-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with the procedure in Example 139(c)-(e) from 1-(3-chlorobenzyl)-5-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester, 2-(4-fluorophenyl)ethylamine and 6-chloro-nicotinoyl chloride.

^{1}H NMR (200 MHz, DMSO-d_6): δ 8.31 (1H, d, *J*=1.9 Hz), 7.82 (1H, s), 7.75 (1H, dd, *J*=8.2, 1.9 Hz), 7.66-7.43 (4H, m), 7.30 (1H, d, *J*=8.2 Hz), 7.21-6.91 (9H, m), 6.38-6.29 (1H, m), 6.06 (1H, d, *J*=16.6 Hz), 5.60 (1H, d, *J*=16.6 Hz), 4.63 (1H, septet, *J*=6.1 Hz), 4.11-3.93 (2H, m), 3.09-2.75 (2H, m), 1.27 (6H, d, *J*=6.1 Hz).

Example 142

Title compounds of the invention were tested in the biological test described above and were found to exhibit 50% inhibition of mPGES-1 at a concentration of 10M or below. For example the inhibition of mPGES-1 is exemplified by the following compounds of the examples, as listed in the following table:

Example 1: 96% inhibition at 10M

Example 2: 100% inhibition at 10M

Example 3: 85% inhibition at 10M

Example 4: 81% inhibition at 10M

Example 5: 93% inhibition at 10M

Example 6: 100% inhibition at 10M